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(54) Title: 95 HUMAN SECRETED PROTEINS

## (57) Abstract

The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

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## 95 Human Secreted Proteins

### *Field of the Invention*

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

### *Background of the Invention*

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include the commercially valuable human insulin, interferon, Factor VIII, human

growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent  
5 medical disorders by using secreted proteins or the genes that encode them.

### ***Summary of the Invention***

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells,  
10 antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

15

### ***Detailed Description***

#### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

20 In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of  
25 matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released  
30 into the extracellular space, the secreted protein can undergo extracellular processing

to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of the coding sequence, but do not comprise all or a portion of any intron. In another embodiment, the nucleic acid comprising the coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene in the genome).

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an

overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

- 5           Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or
- 10   temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent
- 15   hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and

20   commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a

25   complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The polynucleotide of the present invention can be composed of any

30   polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of

single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation,

gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

5 (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

10 "SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the  
15 present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not  
20 more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

### **Polynucleotides and Polypeptides of the Invention**

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 1**

This gene is expressed primarily in anergic T cells and merkel cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders and inflammatory diseases. Similarly, polypeptides

and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 108 as residues: Ala-55 to Gln-64.

The tissue distribution in T-cells and merkel cells indicates that the protein products of this gene are useful for the diagnosis and/or treatment of immune system diseases. Furthermore,

15 Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by  
20 boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune  
25 deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a  
30 tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2329 of SEQ ID NO:11, b is an integer of 15 to 2343, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: IPENRRPASXCTWSMWTSRTTTTRPPWGRFSSVSSASV SSTRKTRWRTRSTSCCRSSRRRVAAPFCTPSASTEPSARMEPPLELPVVHTFSFLTFVFTYRCSAGDGSITQINCA YEMGEEMPKRQMKAIKFLLFHFYL (SEQ ID NO:205), IPENRRPASXCTWSMWTSRTTTTRPPWGRFSSVSSASVSST (SEQ ID NO:206), RKTWRTRSTSCCRSSRRRVAAPFCTPSASTEPSARMEPPLELP (SEQ ID NO:207), and/or VVHTFSFLTTFVFTYRCSAGDGSITQINCA YEMGEEMPKRQ MKAIKFLLFHFYL (SEQ ID NO:208). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in placental, brain and breast tissues, and to a lesser extent in T cells and tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative and/or endocrine disorders and neoplasias, or developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurodegenerative, developing, endocrine and



immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, endocrine, immune, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken  
5 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 109 as residues: Ala-55 to Asn-60, Lys-65 to Met-71, Leu-75 to Asn-86, Asp-93 to  
10 Asp-110, Leu-130 to Cys-138, Gln-149 to Glu-154, Thr-172 to Ile-179, Glu-185 to Arg-192.

The tissue distribution in breast and brain tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of endocrine disorders, neurodegenerative disorders, developmental disorders, immune system  
15 diseases and neoplasias. The tissue distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be  
20 produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus.

Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in  
25 vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Likewise,

Expression of this gene product in T-cells indicates a role in the regulation of  
30 the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be

involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as  
5 well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have  
10 commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders  
15 such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of  
20 developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
30 formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:12, b is an

integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 3

5 The translation product of this gene shares sequence homology with bovine beta-mannosidase, which is thought to be important in lysosomal catabolism of glycoproteins. See, for example, J. Biol. Chem. 270, 3841-3848 (1995), incorporated herein by reference in its entirety. Based on the sequence similarity between these proteins the translation product of this gene will sometimes hereinafter be referred to  
10 as human beta-mannosidase. Human beta-mannosidase is expected to share certain biological activities, particularly enzymatic activities, with bovine beta-mannosidase. Such activities may be assayed by methods known in the art, described in J. Biol. Chem. 270, 3841-3848 (1995), and/or disclosed elsewhere herein.

In specific embodiments, polypeptides of the invention comprise the following  
15 amino acid sequences: HPSIIWSGNNENEEALMMNWHISFTDRPIYIKDYVTL YVKNIRELVLAGDKSRPFITSSPTNGAETVAEAWVSQNPNSNYFGDVHFDYDI SDCWNWKVFPKARFASEYGYQSWPSFSTLEKVSSTEDWSFNKFSLSLRQHH EGGNKQMLYQAGLHFKLPQSTDPLRTFKDTIYLTQVMQAQCVKTETEFYRRS RSEIVDQQGHTMGALYWQLNDIWQAPSW (SEQ ID NO:209), and/or  
20 VRVHTWS SLEPVCSRVTFRFVMKGGAEVCLYEPPVSELLRRCGNCTRESCVVSFYLSAD HELLSPTNYHFLSSPKEAVGLCKAQITAIISQQGDIFVFDLETSAPFVWLDV GSIPGRFSDNGFLMTEKTRTILFYWPWEPTSKNELEQSFHVTSLTDIY (SEQ ID NO:210). Polynucleotides encoding these polypeptides are also encompassed by the  
25 invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in colon tissue, and to a lesser extent in thymus stromal cells and chondrosarcoma tissue.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chondroma and mannosidosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the chondro and immune system. The expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, metabolic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to bovine beta-mannosidase indicates that the protein products of this gene are useful for the diagnosis and/or treatment of chondroma and mannosidosis. Human beta-mannosidosis is an autosomal recessive, lysosomal storage disease caused by a deficiency of the enzyme beta-mannosidase. Furthermore, the homology of the translation product of this gene to beta-mannosidase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as lysosomal storage deficiencies, Tay-Sachs disease, phenylketonuria, galactosemia, hyperlipidemias, porphyrias, and Hurler's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2093 of SEQ ID NO:13, b is an

integer of 15 to 2107, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 4

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: PRLTPRMKWPTAALASRLLGWTVLRPPYPRVPSLPQVT LHPTDGLMAVLYTGGEGR TLGEQHFFHETFVTRWLLGPVPVRFGACSP LSFL APRRGQGAPAGXFCACPRPASRQLCPWPALPGTPYSNSAPLCTGMGHSNTPQ GPPSPQYALSPTEPTSLSGNSHLPAILVL (SEQ ID NO:211),  
 10 PRLTPRMKWPTAAL ASRLLGWTVLRPPYPRVPSLPQVTLHP (SEQ ID NO:212), TDGLMAVLYTGGE GRTLGEQHFFHETFVTRWLLGPVPVRFG (SEQ ID NO:213), ACSPLSFLAPRRGQGAPAGXFCACPRPAS RQLCPWPALPGTP (SEQ ID NO:214), and/or  
 15 YSNSAPLCTGMGHSNTPQGPPSPQYALSPTEPTSLSGNS HLPAILVL (SEQ ID NO:215). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human lung (adult and fetal), and to a lesser extent in liver and brain tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary disorders and hemostasis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
 25 disorders of the above tissues or cells, particularly of the lung and liver tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a  
 30 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 111 as residues: Arg-28 to Gln-36.

The tissue distribution in lung and liver tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of pulmonary disorders and hematopoietic disorders. The tissue distribution in adult and fetal lung tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Alternatively,

Expression of this gene product in liver tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
5 formula of a-b, where a is any integer between 1 to 1248 of SEQ ID NO:14, b is an integer of 15 to 1262, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 5

10 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: HLLVTPCRLPVPEFPGRTPRGSRTPD (SEQ ID NO:216). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in rapidly dividing liver tissue; (e.g., hepatoma, hepatocellular carcinoma, and fetal liver tissue), and to a lesser extent in  
15 normal liver tissue, and other tumors such as colon cancer and uterine cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, particularly hepatomas, colon cancer, and uterine cancer.

20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, colon and uterus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, colon, uterus,  
25 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 112 as residues: Trp-35 to Trp-45, Pro-52 to Asp-57, Thr-73 to Arg-82, Pro-105 to Leu-112, Pro-115 to Arg-127, Pro-140 to Gln-151.

5 The tissue distribution in liver tissues and cancers thereof, as well as other cancerous tissues, indicates that the protein products of this gene are useful for the diagnosis and/or treatment of cancers, particularly, hepatoma, colon cancer and uterine cancer, as well as cancers of other tissues where expression has been observed. Furthermore, expression within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 745 of SEQ ID NO:15, b is an integer of 15 to 759, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 6**

This gene is expressed primarily in hepatocellular tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatomas. Similarly, polypeptides and antibodies directed to these

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polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 113 as residues: Pro-32 to Gly-40.

The tissue distribution in hepatocellular tumors indicates that the protein products of this gene are useful for the diagnosis and/or treatment of hepatomas, as well as cancers of other tissues where expression has been observed. Furthermore, expression within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1796 of SEQ ID NO:16, b is an integer of 15 to 1810, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 7**

This gene is expressed primarily in human rhabdomyosarcoma tissue, as well as in placental tissue.

5           Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, malignant neoplasms and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
15 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:  
20 114 as residues: Arg-23 to Trp-28, Phe-93 to Lys-98, Arg-199 to Trp-206, Gly-208 to Met-213.

The tissue distribution in placental tissue and human rhabdomyosarcoma tissue indicates that the protein products of this gene are useful for the diagnosis and/or treatment of skeletal and reproductive disorders. Furthermore, the tissue  
25 distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then  
30 transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus.

Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1038 of SEQ ID NO:17, b is an integer of 15 to 1052, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 8

This gene is expressed primarily in fetal liver/spleen and fetal skin tissues, and to a lesser extent in breast cancer tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders and neoplasias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal tissue and adult immune system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g., developing, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver/spleen and skin tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of developmental disorders and malignant neoplasias. Likewise, expression within fetal tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, fetal development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy.

15 Alternatively, the tissue distribution in fetal skin tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

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Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1116 of SEQ ID NO:18, b is an integer of 15 to 1130, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 9

The translation product of this gene shares sequence homology with the bacterial *gufA* gene, as well as a *C. elegans* protein of unknown function.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: MIPGSDSQTALNFGSTLMKKKSDPEGPALLFPESELSIRI GRAGLLSDKSENGEAYQRKKAAATGLPEGPAVPVPSRGNLAQPGGSSWRRI ALLILAITIHNVPEGLAVGVGFGAIEKTASATFESARNLAIGIGIQNFPEGLAVS LPLRGAGFSTWRAFWYGQLSGMVEPLAGVFGAFVLAEPILPYALAF AAG AMVYVVMDDIPEAQISGNGKLASWASILGFVVMMSLDVGLG (SEQ ID NO:217), MIPGSDSQTALNFGSTLMKKKSDPEGPALLFPESELSIRIGRA (SEQ ID NO:218), GLLSDKSENGEAYQRKKAAATGLPEGPAVPVPSRGNLAQPG ( S E Q I D N O : 2 1 9 ) , GSSWRRIALLILAITIHNVPEGLAVGVGFGAIEKTASATFESAR (SEQ ID NO:220), NLAIGIGIQNFPEGLAVSLPLRGAGFSTWRAFWYGQLS GMVEP (SEQ ID NO:221), LAGVFGAFVLAEPILPYALAF AAGAMVYVVMDDIPEAQIS (SEQ ID NO:222), and/or GNGKLASWASILGFVVMMSLDVGLG (SEQ ID NO:223). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in cells of the immune system, particularly macrophage.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune system, such as AIDS, as well as

5 inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
10 types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in immune cells such as macrophage indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages,  
20 including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
25 and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of  
30 various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in macrophage also strongly indicates a role

for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 869 of SEQ ID NO:19, b is an integer of 15 to 883, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 10**

This gene is expressed primarily in the spleen metastatic melanoma tissue as well as in embryonic tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the spleen or immune system, developmental disorders, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above  
25 tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., spleen, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
30 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 117 as residues: Asn-37 to Lys-44, Ser-73 to Glu-78, Ala-103 to Ser-111.

The tissue distribution in spleen metastatic melanoma and embryonic tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of disorders affecting the spleen, including cancers of the spleen, as well as cancers of other tissues where expression has been observed. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 975 of SEQ ID NO:20, b is an integer of 15 to 989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 11**

It has been discovered that this gene is expressed primarily in cells of the immune system, including monocytes and neutrophils.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders affecting the immune



system, such as AIDS. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 118 as residues: Ser-12 to Asp-20, Gly-22 to Gly-32, Ala-49 to Thr-57.

The tissue distribution in monocytes and neutrophils indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune system disorders, including AIDS. Furthermore, expression of this gene product in monocytes and neutrophils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in monocytes and neutrophils also strongly suggests a role for this protein in immune function and immune surveillance. Protein,

as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 481 of SEQ ID NO:21, b is an integer of 15 to 495, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

## **15 FEATURES OF PROTEIN ENCODED BY GENE NO: 12**

It has been discovered that this gene is expressed primarily in cells of the immune system, including monocytes.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders affecting the immune system. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 119 as residues: Glu-35 to Trp-42.

The tissue distribution suggests that the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in monocytes suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all  
5 hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as  
10 well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have  
15 commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in monocytes also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or  
20 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
25 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2303 of SEQ ID NO:22, b is an integer of 15 to 2317, where both a and b correspond to the positions of  
30 nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 13**

It has been discovered that this gene is expressed primarily in cells of the immune system, including monocytes.

5           Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of the immune system. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell  
10   type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
15   expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in monocytes indicates that the protein products of this clone are useful for the diagnosis and/or treatment of disorders of the immune system. Expression of this gene product in monocytes suggests a role in the regulation of the  
20   proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

25           Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory  
30   bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of

various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in monocytes also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1712 of SEQ ID NO:23, b is an integer of 15 to 1726, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 14**

The translation product of this gene shares sequence homology with a gene from *C. elegans* of unknown function.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: TRPITYVLLAG (SEQ ID NO:224). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

It has been discovered that this gene is expressed primarily in fetal lung, liver, spleen and heart tissues, as well as adult liver, bladder, endometrial stromal cells, synovium, colon cancer, smooth muscle, keratinocytes, and the bone marrow derived cell line RS4;11.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of the musculo-skeletal system, and cancers of the immune system. Similarly, polypeptides and antibodies  
5 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the musculo-skeletal and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, musculo-skeletal, cancerous and wounded  
10 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in tissues of the immune system indicates that the  
15 protein products of this clone are useful for treating proliferative disorders of immune system precursor cells. Alternatively, the tissue distribution in smooth muscle and heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound  
20 healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 515 of SEQ ID NO:24, b  
30 is an integer of 15 to 529, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 15

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: GTSLTAPLLEFLLALYFLFADAMQLNDKWQGLCWP (SEQ ID NO:225). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 It has been discovered that this gene is expressed primarily in T-cells, fetal spleen and infant brain tissues, and to a lesser extent in many other tissues including melanocytes, lung cancer, macrophages, dendritic cells, stromal cells, adrenal gland and others.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
15 diagnosis of the following diseases and conditions: inflammation and autoimmunity, developing tissues. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developing system, expression of this gene at  
20 significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

25 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 122 as residues: Ser-46 to Gly-51.

The tissue distribution in T-cells and other immune cells indicates that the protein products of this clone are useful for treating diseases involving the activation of T-cells, including inflammation and autoimmune diseases. Alternatively, the tissue  
30 distribution in a wide range of fetal tissues suggests that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and

treatment of cancer and other proliferative disorders. Similarly, fetal development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as,  
5 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of  
10 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1741 of SEQ ID NO:25, b  
15 is an integer of 15 to 1755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 16**

20 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: LANFZCSDCAQTVLFLVLFZILVFTYEIPF (SEQ ID NO:226). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 13. Accordingly, polynucleotides related to this invention are useful as a  
25 marker in linkage analysis for chromosome 13. Recently another group published this gene, referring to it as CLN5 (See Genbank Accession No.: 3342386).

It has been discovered that this gene is expressed primarily in placental tissue, 12 week embryos, and tumors including testes, tongue and pharynx, and to a lesser extent in adipose tissue, tonsils, melanocytes, fetal spleen, macrophages, T-cells,  
30 amniotic cells, and brain tissue.



Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: tumors, particularly of the tongue and throat, and neurodegenerative disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and digestive systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., tongue, throat, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 123 as residues: Pro-44 to Ala-60, Val-187 to Thr-193, Lys-203 to Ala-210, Thr-212 to Cys-219.

The tissue distribution in tongue and pharynx carcinoma tissue indicates that the protein products of this clone are useful for diagnosing and/or treating oral cancers, including tumors of the throat and tongue. Furthermore, the tissue distribution in brain tissue suggests that the protein product of this clone is useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as neuronal ceroid lipofuscinoses (NCLs), Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1737 of SEQ ID NO:26, b is an integer of 15 to 1751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 17**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

QAWHEVGGGVRRRCWFVLGERRAGSLLSASYGTFAMPG

MVLFGRRWAIASDDLVPFGFFELVVRVLWWIGILTLYL (SEQ ID NO:227),  
and/or PGMVLFGRRWAIASDDLVPFGFFELVVRVLWWIGILTLYLMHRGKLD  
CAGGALLSSYLIVLMILLAVVICTVSAIMCVSMRGTCNPGPRKSMKLLYIRL  
ALFFPEMVWASLGAAWVADGVQCD (SEQ ID NO:228). Polynucleotides  
encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed in activated neutrophils, infant brain tissue and primary dendritic cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of the immune system, and neurodegenerative disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and neural systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual

having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 124 as residues: Pro-47 to Met-53, Ser-130 to Ser-138.

5       The tissue distribution in neutrophils and primary dendritic cells indicates that the protein products of this clone are useful for diagnosing and/or treating immune system disorders. Expression of this gene product in neutrophils and primary dendritic cells suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem  
10 cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
15 and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of  
20 various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils and primary dendritic cells also strongly suggests a role for this protein in immune function and immune surveillance.

Alternatively, the tissue distribution in brain tissue suggests that the protein product of this clone is useful for the detection/treatment of neurodegenerative  
25 disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play  
30 a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1198 of SEQ ID NO:27, b is an integer of 15 to 1212, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 18**

It has been discovered that this gene is expressed primarily in neutrophils, and to a lesser extent in other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 125 as residues: Gln-17 to Ser-24.

The tissue distribution in neutrophils indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and inflammatory disorders. Expression of this gene product in neutrophils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of  
5 potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as  
10 well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have  
15 commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or  
20 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
25 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1098 of SEQ ID NO:28, b is an integer of 15 to 1112, where both a and b correspond to the positions of  
30 nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 19**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: HERNCFPMWLNHSAFPPV (SEQ ID NO:229).

- 5 Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in neutrophils, and to a lesser extent in other tissues.

- Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
10 diagnosis of the following diseases and conditions: immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels  
15 may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

- 20 The tissue distribution in neutrophils indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and inflammatory disorders. Expression of this gene product in neutrophils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene  
25 product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

- Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
30 and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune

deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 734 of SEQ ID NO:29, b is an integer of 15 to 748, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

20

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 20**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: GWTRENDHRALSKAGIGSAEIQPSNLRVGS AKDLGKPW AGKLLLLSSCLLFFSLGVLYRGQMLAPPLQEDWKGGVKDSDLIDDSSASPIPP SYLEYKAALYPFSEHKSVRNATDSLTFVLVTDHFLDNQDSQ (SEQ ID NO:230), GWTRENDHRALSKAGIGSAEIQPSNLRVGS AKDLGKPWAGKLLLL (SEQ ID NO:231), SSCLLFFSLGVLYRGQMLAPPLQEDWKGGVKDSDLIDDSSASPIPP (SEQ ID NO:232), and/or SYLEYKAALYPFSEHKSVRNATDSLTFVLVTDHFL DNQDSQ (SEQ ID NO:233). Polynucleotides encoding these polypeptides are also encompassed by the invention.

30

It has been discovered that this gene is expressed primarily in ovarian cancer tissue, and to a lesser extent in other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: ovarian cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ovaries, expression of this gene at significantly higher or lower levels may be detected in  
10 certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 127 as residues: Thr-20 to Gly-27, Gly-32 to Phe-41.

The tissue distribution in ovarian cancer tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of ovarian cancer, as well as cancers of other tissues where expression has been observed. Protein, as  
20 well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 764 of SEQ ID NO:30, b  
30 is an integer of 15 to 778, where both a and b correspond to the positions of



nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 21

5        When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent other cells, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The  
10    Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

      In specific embodiments, polypeptides of the invention comprise the following  
15    amino acid sequences: LKFHQESLSGD (SEQ ID NO:234). Polynucleotides encoding these polypeptides are also encompassed by the invention.

      It has been discovered that this gene is expressed primarily in fast-growing tissues such as immune/hematopoietic tissues, early developmental stage human tissues, and tumor tissues, and to a lesser extent in some other tissues.

20        Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: growth disorders, immune and inflammatory diseases, and tumorigenesis. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for  
25    differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune/hematopoietic system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an  
30    individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 128 as residues: Glu-60 to Arg-65.

The tissue distribution in immune tissues, in conjunction with the biological activity data, indicates that the protein products of this clone are useful for the diagnosis and/or treatment of growth disorders, immune and inflammatory diseases, and tumorigenesis. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells suggests that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1310 of SEQ ID NO:31, b is an integer of 15 to 1324, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 22**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: EAKSRPVTQAGVQWHDLGSLQPLPP (SEQ ID NO:235).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in ovarian cancer tissue, and to a lesser extent in fetal liver/spleen and retinal tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: ovarian cancer, immune disorders, and retinal disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ovaries, immune and ocular systems, expression of this gene at  
10 significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, ovaries, retina, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 The tissue distribution in ovarian cancer tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of ovarian cancer, as well as cancers of other tissues where expression has been observed. The tissue distribution also suggests that the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this  
20 gene product in fetal liver/spleen suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune  
25 responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune  
30 deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have

commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in retinal tissue suggests that the protein product of this clone is useful for the treatment and/or detection of eye disorders including blindness, color blindness, impaired vision, short and long sightedness, retinitis pigmentosa, retinitis proliferans, and retinoblastoma, retinoblastoma, retinopathy and retinoschisis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 725 of SEQ ID NO:32, b is an integer of 15 to 739, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 23

The translation product of this gene shares sequence homology with a C. elegans protein of unknown function (See Genbank Accession No.: gnllPID1348017). When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The gene encoding the disclosed cDNA is thought to reside on

chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: EAKSRPVTQAGVQWHDLSLQPLPP (SEQ ID NO:236),  
5 and/or ALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPSELELDDVVIT  
NPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMKTSA  
SVSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDAR (SEQ ID NO:237).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in fast growing  
10 tissues such as early development stage human tissues, immune/hematopoietic  
tissues, melanocytes, and tumor tissues, and to a lesser extent in some other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential  
identification of the tissue(s) or cell type(s) present in a biological sample and for  
diagnosis of the following diseases and conditions: growth disorders, immune and  
15 inflammatory disorders, skin and connective tissue disorders, and tumorigenesis.  
Similarly, polypeptides and antibodies directed to those polypeptides are useful to  
provide immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the fast  
growing tissues such as early development stage human tissues,  
20 immune/hematopoietic tissues, skin and connective tissue, and tumor tissues,  
expression of this gene at significantly higher or lower levels may be detected in  
certain tissues or cell types (e.g., musculo-skeletal, skin, immune, developing,  
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
synovial fluid or spinal fluid) taken from an individual having such a disorder,  
25 relative to the standard gene expression level, i.e., the expression level in healthy  
tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
130 as residues: Pro-34 to Ser-43, Glu-54 to Ser-60.

The tissue distribution suggests that the protein product of this clone is useful  
30 for the diagnosis and/or treatment of growth disorders, immune and inflammatory  
disorders, and tumorigenesis. Alternatively, the tissue distribution in melanocytes, in

conjunction with the observed biological activity data, suggests that the protein product of this clone is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. 5 keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, 10 pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma.

Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, 15 and ringworm). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are 20 related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the 25 general formula of a-b, where a is any integer between 1 to 1448 of SEQ ID NO:33, b is an integer of 15 to 1462, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 24**

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent other cells, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

DVESRGPSARCLPVVPGSLLPGLEPATKLM PGGLAPGHG  
 APVRELLLPLLSQPTLGSLWDSLRHCSLLCNPLSCVPALEAPPSLVSLGCSGGC  
 15 PRLSLAGSASFPFLTALLSLLNTLAQIHKGLCGQLAAILAAPGLQNYFLQCVA  
 PGAAPHLTPFSAWALRHEYHLQYLALALAQAALQPLPATHAALYHGMAL  
 ALLSRLLPGSEYLTHELLLSCVFRLEFLPERTSGGPEAADFSDQLSLGSSRVPR  
 CGQGTLAQAQCDLPSIRNCYLTHCSPARASLLASQALHRGELQRVPTLLLP  
 MPTPELLPTDWPFLH (SEQ ID NO:238),  
 20 DVESRGPSARCLPVVPGSLLPGLEPATKLM PGGLAPGHGAPVRE (SEQ ID  
 NO:239), LLLPLLSQPTLGSLWDSLRHCSLLCNPLSCVPALEAPPSLVSLGC  
 (SEQ ID NO:240), SGGCPRLSLAGSASFPFLTALL  
 SLLNTLAQIHKGLCGQLAAILA (SEQ ID NO:241), APGLQNYFLQCVAPGAAP  
 HLTPFSAWALRHEYHLQYLALALAQA (SEQ ID NO:242), AAALQPLPATHAA  
 25 LYHGMALALLSRLLPGSEYLTHELLLSCVFR (SEQ ID NO:243), LEFLPERTSG  
 GPEAADFSDQLSLGSSRVPRCGQGTLAQAQCDL (SEQ ID NO:244), and/or  
 PSIRNCYLTHCSPARASLLASQALHRGELQRVPTLLLPMPTEPELLPTDWPFLH  
 (SEQ ID NO:245). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

It has been discovered that this gene is expressed primarily in hematopoietic tissues and fetal heart tissue, and to a lesser extent in brain and gall bladder tissues, and some other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential  
5 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and inflammatory disorders, cardiovascular disorders, and growth disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
10 of the above tissues or cells, particularly of the hematopoietic and vascular systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., vascular, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
15 expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 131 as residues: Tyr-88 to Trp-102, Asp-105 to Ser-110.

The tissue distribution in hematopoietic tissues, in conjunction with the  
20 observed biological activity data, indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and inflammatory disorders and growth disorders. Alternatively, the tissue distribution in fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease,  
25 restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
30 related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically



excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2801 of SEQ ID NO:34, b  
5 is an integer of 15 to 2815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 25**

10 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: VGSVLGAFLTFPGLRLAQTHRDALT (SEQ ID NO:246). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in  
15 linkage analysis for chromosome 19.

It has been discovered that this gene is expressed primarily in human pituitary tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
20 diagnosis of the following diseases and conditions: hyperpituitarism and hypopituitarism. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or  
25 lower levels may be detected in certain tissues or cell types (e.g., endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. This gene is found on the short arm  
30 of chromosome 19 and, therefore, is useful as a chromosome marker.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 132 as residues: Met-1 to Pro-6, Gln-89 to Ala-94, Pro-161 to Cys-173.

The tissue distribution in pituitary tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of pituitary disorders. More generally, the tissue distribution in pituitary tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1064 of SEQ ID NO:35, b is an integer of 15 to 1078, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

## **25 FEATURES OF PROTEIN ENCODED BY GENE NO: 26**

It has been discovered that this gene is expressed highly and specifically in placental and bone marrow cDNA libraries, and to a lesser extent in T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune, developmental and reproductive disorders. Similarly, polypeptides and antibodies directed to those

polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developing systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, developmental, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

10           The tissue distribution in bone marrow and placental tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and reproductive disorders. The tissue distribution in bone marrow suggests that the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

          Alternatively, the tissue distribution in placental tissue suggests that the protein product of this clone is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta suggests that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus.

          Expression of this gene product in a vascular-rich tissue such as the placenta also suggests that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in

vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1203 of SEQ ID NO:36, b is an integer of 15 to 1217, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 27**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

LECTDTIMVHCSLKLLSPSDXSHSASQVAKTRGVHHXTQ

LIFKVFFVXMGSHSTKYXSIRPGLLP (SEQ ID NO:247). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human prostate and smooth muscle tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders in the prostate gland, vascular and connective tissues. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive and urinary system and vascular system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, vascular, cancerous and wounded  
5 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in prostate and smooth muscle tissues indicates that the  
10 protein products of this clone are useful for the diagnosis and/or treatment of prostate gland, vascular and connective tissue disorders. The tissue distribution in smooth muscle tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound  
15 healing. The expression in the prostate tissue may indicate the gene or its products can be used in the disorders of the prostate, including inflammatory disorders, such as chronic prostatitis, granulomatous prostatitis and malacoplakia, prostatic hyperplasia and prostate neoplastic disorders, including adenocarcinoma, transitional cell carcinomas, ductal carcinomas, squamous cell carcinomas, or as hormones or factors  
20 with systemic or reproductive functions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
30 general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:37, b is an integer of 15 to 1282, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 28**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: ESSFVPPAAHSSLC (SEQ ID NO:248). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 It has been discovered that this gene is expressed primarily in human pituitary tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: hyperpituitarism and  
10 hypopituitarism. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., endocrine,  
15 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in pituitary tissue indicates that the protein products of  
20 this clone are useful for the diagnosis and/or treatment of pituitary gland disorders such as hypopituitarism and hyperpituitarism. More generally, the tissue distribution in pituitary tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of  
25 the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 545 of SEQ ID NO:38, b is an integer of 15 to 559, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 29

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

LLPGQQEATQCVEAGAGEGALTPMCPCRQEQFVDLYKEF

EPSLVNSTVYIMAMAIQMAPFAINYKVRPGPCXNIHCLPTQPHPMKPSVPHPH  
 RARPSWRACPRTSPWCGVWQFHSWPSLACSSAPRPTSTASLASWTSLWSSS  
 WSLPRSCSWTSAWRSWPTASCSSSWGPRS (SEQ ID NO:249),  
 LLPGQQEATQCV EAGAGEGALTPMCPCRQEQFVDLYKEFEPSTVN (SEQ ID  
 NO:250), STVYIMAMAIQMAPFAINYKVRPGPCXNIHCLPTQPHPMKPSVP  
 (SEQ ID NO:251),  
 HPHRARPSWRACPRTSPWCGVWQFHSWPSLACSSAPRPTSTA (SEQ ID  
 NO:252), and/or SLASWTSLWSSSWSLPRSCSWTSAWRSWPTASCSSSWG PRS  
 (SEQ ID NO:253). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human pituitary and breast tissues, and to a lesser extent in endometrial and ovarian cancer tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: hyperpituitarism and hypopituitarism, and cancers of the female reproductive system. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide



immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and reproductive systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., endocrine, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 136 as residues: Ser-3 to Lys-8.

The tissue distribution in pituitary tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of disorders in the pituitary gland. More generally, the tissue distribution in pituitary tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Alternatively, the tissue distribution in breast tissue and cancerous tissues of the endometrium and ovaries suggests that the translation product of this gene is useful for the detection and/or treatment of disorders and cancers of the female reproductive system, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 789 of SEQ ID NO:39, b is an integer of 15 to 803, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

5

### FEATURES OF PROTEIN ENCODED BY GENE NO: 30

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: TRNLSFIKCVIHNFWIPKESNEITHINPYRETVCFVSVEPVKKIFNY (SEQ ID NO:254). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10

It has been discovered that this gene is expressed primarily in human synovial sarcoma tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., skeletal, connective, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15

20

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 137 as residues: Thr-29 to Pro-34.

25

The tissue distribution in synovial sarcoma tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of diseases of the synovium. In addition, the

Expression of this gene product in synovium suggests a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma,

30

tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1496 of SEQ ID NO:40, b is an integer of 15 to 1510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

## 20 **FEATURES OF PROTEIN ENCODED BY GENE NO: 31**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: LVVLFASSNSRYLK YFFLVPLILGSAW (SEQ ID NO:255). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human rhabdomyosarcoma and fetal liver/spleen tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: malignant neoplasms and hematopoiesis. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the skeletal and immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., musculo-skeletal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 138 as residues: Gly-29 to Thr-35.

The tissue distribution in rhabdomyosarcoma and fetal liver/spleen tissues indicates that the protein products of this clone are useful for diagnosis and treatment of skeletal and immune disorders. The expression in rhabdomyosarcoma tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various muscle disorders, such as muscular dystrophy, cardiomyopathy, fibroids, myomas, and rhabdomyosarcomas. Alternatively,

Expression of this gene product in fetal liver/spleen tissue suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
5 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1081 of SEQ ID NO:41, b is an integer of 15 to 1095, where both a and b correspond to the positions of  
10 nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 32**

It has been discovered that this gene is expressed primarily in fibrosarcoma  
15 tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: fibrosarcoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide  
20 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the connective tissue system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., musculo-skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or  
25 spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 139 as residues: Ser-34 to Gln-40, Gly-42 to Glu-48, Tyr-56 to Leu-62.

30 The tissue distribution in only fibrosarcoma tissue suggests that the protein product of this clone is useful for the treatment, diagnosis and/or prognosis of

fibrosarcoma's or other disorders related with fibrous tissue including fibroma, fibromatosis, fibromyoma, fibromyositis, fibrosis and fibrositis. Likewise, the expression in fibrosarcoma tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various muscle disorders, such as muscular dystrophy, cardiomyopathy, myomas, and rhabdomyosarcomas. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1148 of SEQ ID NO:42, b is an integer of 15 to 1162, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

## **20 FEATURES OF PROTEIN ENCODED BY GENE NO: 33**

It has been discovered that this gene is expressed primarily in Hodgkins lymphoma and breast cancer tissues, and to a lesser extent in stromal cells and brain tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: lymphoma, breast cancer, and neurological disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types

(e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 140 as residues: Pro-22 to Lys-29.

The tissue distribution in Hodgkins lymphoma, brain and breast cancer tissues suggests a role in the treatment, diagnosis and/or prognosis of breast cancer, immune and hematopoietic disorders including arthritis, asthma, immunodeficiency diseases, 10 leukemia and Hodgkin's lymphoma and neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed 15 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically 20 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:43, b is an integer of 15 to 657, where both a and b correspond to the positions of 25 nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 34**

In specific embodiments, polypeptides of the invention comprise the following 30 amino acid sequences: HEWKCKQKYSESGNTRIGN (SEQ ID NO:256).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in chronic synovitis tissue, and to a lesser extent in fetal kidney and testes tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: synovitis, renal disorders and male infertility. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the connective tissue system, the renal system, and the male reproductive system,  
10 expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., skeletal, renal, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not  
15 having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 141 as residues: Met-33 to Pro-39, Ser-74 to Trp-79.

The tissue distribution of this gene in chronic synovitis, testes, and kidneys suggests a role in the treatment, diagnosis and prognosis of synovial membrane  
20 disorders including synovitis, renal disorders including kidney failure, renal colic, renal diabetes, hypertension, osteodystrophy, tubular acidosis and kidney stones; and and male infertility. Furthermore, the tissue distribution in testes tissue indicates that the protein product of this clone is useful for the treatment and/or diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm  
25 maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene  
30 expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific



tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. In addition, the

Expression of this gene product in synovium suggests a role in the detection  
5 and/or treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and  
10 specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
20 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1141 of SEQ ID NO:44, b is an integer of 15 to 1155, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a  
25 + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 35**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: LLPLCFLGPRQVLEEFPSIV (SEQ ID NO:257).

30 Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in brain tissue, and to a lesser extent in osteoclastoma and testes tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: neurological disorders and male reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system and the male reproductive system, expression of  
10 this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 The tissue distribution of this gene in brain tissue suggests a role in the diagnosis, prognosis and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the  
20 treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
30 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1098 of SEQ ID NO:45, b

is an integer of 15 to 1112, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 36

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: PTRPSKHQEAGS (SEQ ID NO:258). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly,  
10 polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

It has been discovered that this gene is expressed primarily in adult and fetal heart tissue, and to a lesser extent in fetal lung and fetal liver/spleen tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential  
15 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: cardiovascular and immune disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
20 the vascular and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., vascular, immune, pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in  
25 healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 143 as residues: Val-2 to Ser-14.

The tissue distribution in heart, fetal liver and fetal spleen tissues suggests a role in the treatment and/or diagnosis of cardiovascular disorders including  
30 myocardial infarction, congestive heart failure, coronary failure, as well as immune disorders including autoimmune diseases, such as lupus, transplant rejection, allergic

reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS.

Furthermore, the tissue distribution in adult and fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stoke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4009 of SEQ ID NO:46, b is an integer of 15 to 4023, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

## **20 FEATURES OF PROTEIN ENCODED BY GENE NO: 37**

It has been discovered that this gene is expressed primarily in testes tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: male infertility and reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the

standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in testes tissues suggests a role in the treatment and/or diagnosis of male infertility, and testicular disorders including cancer. Furthermore, the tissue distribution in testes tissue indicates that the protein product of this clone is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 528 of SEQ ID NO:47, b is an integer of 15 to 542, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 38**

It has been discovered that this gene is expressed primarily in apoptotic T-cells, and to a lesser extent in brain tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential  
5 identification of the tissue(s) or cell type(s) present in a biological sample and for  
diagnosis of the following diseases and conditions: immune and neurological  
disorders. Similarly, polypeptides and antibodies directed to those polypeptides are  
useful to provide immunological probes for differential identification of the tissue(s)  
or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
10 the immune and nervous systems, expression of this gene at significantly higher or  
lower levels may be detected in certain tissues or cell types (e.g., immune, neural,  
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
synovial fluid or spinal fluid) taken from an individual having such a disorder,  
relative to the standard gene expression level, i.e., the expression level in healthy  
15 tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
145 as residues: Glu-33 to Tyr-42.

The tissue distribution in apoptotic T-cells suggests potential roles in the  
treatment and/or diagnosis of immune disorders including of immune and  
20 autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis,  
asthma, immunodeficiency diseases, leukemia, and AIDS. Alternatively, expression  
in brain tissue suggests a role in the treatment and/or diagnosis of neurodegenerative  
disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's  
Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive  
25 compulsive disorder and panic disorder. Furthermore, the tissue distribution in  
apoptotic T-cells indicates that the translation product of this gene may also be  
involved in apoptosis or tissue differentiation and could again be useful in cancer  
therapy. Protein, as well as, antibodies directed against the protein may show utility as  
a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly  
available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1481 of SEQ ID NO:48, b is an integer of 15 to 1495, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 39**

The translation product of this gene shares sequence homology with phosphomannomutase, which is thought to be important in mannose metabolism.

It has been discovered that this gene is expressed primarily in meningioma and testis tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: meningioma related diseases. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 146 as residues: Ser-33 to Lys-43.

The tissue distribution in meningioma, and the homology to phosphomannomutase, suggests that the protein product of this clone is useful for the

diagnosis and/or intervention of meningioma related diseases. For example, the gene product can be used for preventing microbial infection of the meninges, for imaging conjugates, or as a secretory factor as a endocrine with systemic, central or peripheral nerve functions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 804 of SEQ ID NO:49, b is an integer of 15 to 818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 40**

It has been discovered that this gene is expressed primarily in tonsils, osteoclastoma and retinoic acid treated teratocarcinoma cells, and to a lesser extent in macrophages, female bladder, adipose tissue, myeloid progenitor cells, prostate tissue, and number of other tissues and organs.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: tonsils and osteoclast related diseases. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and bone systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,



synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
5 147 as residues: Glu-55 to Arg-61, Gln-84 to Ser-92, Ser-99 to Ser-104.

The tissue distribution in tonsils and osteoclastoma suggests that the protein product of this clone is useful for the diagnosis and/or intervention of diseases related to tonsils or osteoclasts. For example, tonsillitis, adenoids, peritonsillar abscess, neoplasms, or bone related disorders like rickets, abnormalities of bone growth and  
10 modelling, fracture, osteonecrosis, and osteoporosis etc. Expression of this gene product in osteoclastoma suggests that it may play a role in the survival, proliferation, and/or growth of osteoclasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis.

Alternatively, the expression of this gene product in tonsils suggests a role in  
15 the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

20 Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory  
25 bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1697 of SEQ ID NO:50, b is an integer of 15 to 1711, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 41**

It has been discovered that this gene is expressed primarily in resting T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: T-cell related disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in resting T-cells suggests that the protein product of this clone is useful for the diagnosis and/or intervention of T-cell related disorders, such as infection, inflammation, allergy, tissue/organ transplantation, immune deficiency etc. Furthermore, the expression of this gene product in T cells also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 735 of SEQ ID NO:51, b is an integer of 15 to 749, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 42

The translation product of this gene shares weak sequence homology with Human metastasis suppressor KiSS-1 fragment, which is thought to be important in the diagnosis, prevention, staging and/or treatment of cancers, such as melanoma (See Accession No. W15789).

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: GQGPAGRWRRLPCSR RAGGERGPHWGVWAGPQM SCGLXFGP (SEQ ID NO:259), WRTQGPMVLLWVVTCPATMLTEPQNPHLIGF VAYSGPSHTTQPHKYWLLLDGQADPAAAEGPVKRKAASVWWWPQALRHLS LLVHCWEESYEMNIGCQSLWAGGLASSGNGWDLGVAFRRDTCMSSSSLHW KEFKYAPGSLHYFALS FVLILTEICLVSSGMGFPQEGKHFSVLGSPDCSLWGR DEHVPREFA (SEQ ID NO:260), WRTQGPMVLLWVVTCPATMLTEPQNPHLIGFVAY SGPSHTTQ (SEQ ID NO:261), PHKYWLLLDGQADPAAAEGPVKRKAASVWW WPQALRHLSLL (SEQ ID NO:262), VHCWEESYEMNIGCQSLWAGGLASSGNGW DLGVAFRRDTCM (SEQ ID NO:263), SSSSLHWKEFKYAPGSLHYFALS FVLILT EICLVSSGMGFPQEG (SEQ ID NO:264), and/or KHFSVLGSPDCSLWGRDEHV PREFA (SEQ ID NO:265). Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

It has been discovered that this gene is expressed primarily in tonsils,  
5 osteoclastoma and teratocarcinoma tissues, and to a lesser extent in female bladder, adipose tissue, myeloid progenitor, prostate tissue, and number of other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: diseases related to tonsils and  
10 osteoclasts. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and bone system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, skeletal,  
15 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in tonsils and osteoclastoma tissues suggests that the  
20 protein product of this clone is useful for the diagnosis and/or treatment of diseases related to tonsils and osteoclasts. For example, tonsillitis, adenoids, peritonsillar abscess, neoplasms, or abnormal growth and modelling of the bone, osteonecrosis, osteoporosis, osteodystrophy, osteoclastoma etc. Expression of this gene product in osteoclastoma suggests that it may play a role in the survival, proliferation, and/or  
25 growth of osteoclasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis.

Moreover, the expression of this gene product in tonsils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene  
30 product may be involved in the regulation of cytokine production, antigen

presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1077 of SEQ ID NO:52, b is an integer of 15 to 1091, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

## 25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 43**

The translation product of this gene shares sequence homology with the Drosophila gene "maleless", which is one of four known regulatory loci required for increased transcription (dosage compensation) of X-linked genes (See Genbank Accession No.: gil157906).

30 It has been discovered that this gene is expressed primarily in normal prostate tissue, testes tissue, whole 6-week old embryonic tissue, human colon carcinoma

(HCC) cell line, and cerebellum tissue, and to a lesser extent in primary breast cancer, activated T-cells, and many other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: diseases of the prostate or colon, or male reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate or colon carcinoma, and male reproductive  
10 disorders, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., colon, prostate, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an  
15 individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 150 as residues: Val-39 to Ala-45.

The tissue distribution in colon and prostate tissues suggests that the protein product of this clone is useful for the diagnosis and/or treatment of prostate disorders  
20 such as prostatitis, prostatic hyperplasia, prostate cancers, or human colon carcinoma, as well as cancers of other tissues where expression has been observed. Alternatively, the tissue distribution in testes tissue, in conjunction with the homology to the *Drosophila* maleless gene, suggests that the translation product of this gene is useful for the detection and/or treatment of disorders involving the testes or the transcription  
25 of X-linked genes. Furthermore, the tissue distribution indicates that the protein product of this clone is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence.

30 This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the

protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2240 of SEQ ID NO:53, b is an integer of 15 to 2254, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 44**

The translation product of this gene shares weak sequence homology with Eimeria antigen Eam45 M3, which is thought to be important in uses as a vaccine for protecting chickens against coccidiosis.

It has been discovered that this gene is expressed primarily in adrenal gland tissue, and to a lesser extent in activated T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: adrenal cortical insufficiency, adrenal cortical hyperfunction, neoplasia. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in adrenal gland tissue suggests that the protein product of this clone is useful for the diagnosis and/or intervention of disorders caused by adrenal gland abnormalities, such as adrenal cortical insufficiency, adrenal cortical hyperfunction, and neoplasia. More generally, the tissue distribution suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 472 of SEQ ID NO:54, b is an integer of 15 to 486, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

30

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 45**



The translation product of this gene shares sequence homology with neural thread protein, tumor necrosis factor related gene product, human alpha-1C2 adrenalin receptor, which is thought to be important for diagnosing the presence of Alzheimer's disease, neuroectodermal tumours and a malignant astrocytoma, or  
5 diagnosis of hepatocellular carcinomas and preneoplastic or pathological conditions of the liver, and tumor immunity.

It has been discovered that this gene is expressed primarily in activated T-cells and endothelial cells.

Therefore, nucleic acids of the invention are useful as reagents for differential  
10 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: Alzheimer's disease, neuroectodermal tumours and a malignant astrocytoma, hepatocellular carcinomas and tumors of various origins. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification  
15 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and endothelial cells, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, endothelial, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual  
20 having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 152 as residues: Arg-38 to Arg-47.

The tissue distribution in immune and endothelial tissues, and the homology to  
25 neural thread protein, tumor necrosis factor related gene product, human alpha-1C2 adrenalin receptor, or Smaller hepatocellular oncoprotein (hhcm) gene product suggests that the protein product of this clone is useful for the diagnosis and/or treatment of tumors of various origins, including neuroectodermal tumours and a malignant astrocytoma, hepatocellular carcinomas, as well as syndromes inflicted by  
30 these cancers. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
5 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1256 of SEQ ID NO:55, b is an integer of 15 to 1270, where both a and b correspond to the positions of  
10 nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 46**

It has been discovered that this gene is expressed primarily in tumor tissues  
15 such as hepatocellular tumor, hemangiopericytoma, chronic lymphocytic leukemia, and activated T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: tumors of various origins.  
20 Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatocellular tumor, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., liver, immune, cancerous and  
25 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in hepatocellular tumors suggests that the protein  
30 product of this clone is useful for the diagnosis and/or targeting of hepatocellular carcinomas, preneoplastic or pathological conditions of the liver, Alzheimer's disease,

neuroectodermal tumours and malignant astrocytoma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2045 of SEQ ID NO:56, b is an integer of 15 to 2059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 47**

It has been discovered that this gene is expressed primarily in glioblastoma, ulcerative colitis, and hemangiopericytoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: glioblastoma, hemangiopericytoma and their inflicted disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain tissues, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 154 as residues: Pro-31 to Ala-37.

The tissue distribution suggests that the protein product of this clone would be useful for the diagnosis, targeting and/or treatment of tumors in the brain, such as glioblastoma and hemangiopericytoma. Additionally, the gene products can be useful agent for the diagnosis and treatment of ulcerative colitis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 854 of SEQ ID NO:57, b is an integer of 15 to 868, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 48**

It has been discovered that this gene is expressed primarily in bone marrow.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and other hematopoietic disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types

(e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 155 as residues: Thr-47 to Val-53.

The tissue distribution in bone marrow suggests that the protein product of this clone is useful for the diagnosis and/or treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-  
10 suppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer. Furthermore, the tissue distribution in bone marrow suggests that the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia,  
15 thrombocytopenia or leukemia.

The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy,  
20 immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
30 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:58, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 49**

It has been discovered that this gene is expressed primarily in bone marrow.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
10 diagnosis of the following diseases and conditions: immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and other hematopoietic disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of  
15 the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in  
20 healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 156 as residues: Leu-40 to Cys-47.

The bone marrow tissue distribution suggests that the protein product of this clone would be useful for the diagnosis and treatment of immune disorders including:  
25 leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immunosuppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer. Furthermore, the tissue distribution in bone marrow suggests that the protein product of this clone is useful for the treatment and diagnosis of  
30 hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia.

The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 681 of SEQ ID NO:59, b is an integer of 15 to 695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 50**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: IAQGTVP LTKRGVQSSGPDYPEGTLTPLPRG (SEQ ID NO:266 and 267). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in dendritic cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune disorders and related conditions such as leukemias, lymphomas, inflammation, hematopoietic dysfunction,

arthritis and asthma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of dendritic cells. For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels  
5 may be detected in certain tissues or cell types (e.g., dendritic cells, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 157 as residues: Ser-25 to Phe-31, Lys-55 to Arg-61.

The tissue distribution in dendritic cells suggests that the protein product of this clone is useful for the diagnosis and/or treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-  
15 suppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer.

Moreover, the expression of this gene product in dendritic cells also strongly suggests a role for this protein in immune function and immune surveillance. Protein,  
20 as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 300 of SEQ ID NO:60, b  
30 is an integer of 15 to 314, where both a and b correspond to the positions of



nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 51

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DCLYLALSFPWHCHCHHHPPSGSLLYPF (SEQ ID NO:268). Polynucleotides encoding these polypeptides are also encompassed by the invention. The translation product of this gene shares sequence homology with a C. elegans protein of unknown function (See Genbank Accession No.: gil1947142  
10 (AF000264)).

It has been discovered that this gene is expressed primarily in healing abdominal wound tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
15 diagnosis of the following diseases and conditions: tissue necrosis, wound healing, ulceration, neoplasms or cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of injured tissue, expression of this gene at significantly  
20 higher or lower levels may be detected in certain tissues or cell types (e.g., vascular, endothelial, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

25 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 158 as residues: Pro-34 to Tyr-43, Gln-73 to Cys-86, Pro-98 to Leu-103.

The tissue distribution in healing abdominal wound tissue suggests that the protein product of this clone is useful for the treatment and/or diagnosis of conditions involving tissue repair and wound healing. Tissue repair may be indicated in cases of  
30 injury to the skin or internal organs, ulceration, cellular necrosis or other conditions involving healing of both diseased or non-diseased, traumatized tissue. In addition,

because of the implications of tissue regeneration, remodeling and growth regulation, the protein product of this gene may have indications in the diagnosis and treatment of neoplasms and cancer.

More generally, the tissue distribution in endothelial tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Likewise, the tissue distribution further suggests that the protein product of this clone is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this clone may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 720 of SEQ ID NO:61, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 52**

The translation product of this gene shares sequence homology with FAR-17A, which is an androgen induced protein, absent in castrated hamsters (See Genbank Accession No.: gil191315), as well as a male hormone-dependent gene product (See GenSeq Accession No.: R10612). The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: ASLPPSRSRPLANMALVPCQVLRMAILLSYCSILCNYKA IEMPSHQTYGGSWKFLTFIDLVIQAVFFGICVLTDLSSLLTRGSGNQEQERQLK KLISLRDW (SEQ ID NO:269). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in fetal liver and spleen tissue, and to a lesser extent in a variety of other fetal tissues and brain tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune disorders including leukemias, lymphomas; reproductive and endocrine disorders, including testicular cancer; and liver disorders (e.g. hepatoblastoma, metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and reproductive systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, reproductive, cancerous  
5 and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
10 159 as residues; Thr-59 to Gly-70, Tyr-132 to Glu-150.

The tissue distribution and homology to FAR-17A suggests that the protein product of this clone is useful for the treatment and/or diagnosis of androgen related conditions and disorders. Male reproductive and endocrine disorders would be potential area of application (e.g. endocrine function, sperm maturation). It may also  
15 prove to be valuable in the diagnosis and treatment of testicular cancer.

More generally, the protein product of this clone may be useful for the treatment and/or diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is  
20 also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other  
25 specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
5 general formula of a-b, where a is any integer between 1 to 1396 of SEQ ID NO:62, b is an integer of 15 to 1410, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

10

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 53**

Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of THP-1 to calcium. Thus it is likely that the product of this gene is involved in a signal transduction  
15 pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of monocytes, and to a lesser extent, in immune or hematopoietic cells and tissues. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocytes.

In specific embodiments, polypeptides of the invention comprise the following  
20 amino acid sequence: MSRSSRISGLSCPWLL (SEQ ID NO:270). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

25 It has been discovered that this gene is expressed primarily in T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and hematopoietic diseases and/or disorders. Similarly, polypeptides and antibodies directed to those  
30 polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the immune and haemopoietic systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 160 as residues: Pro-42 to Cys-50, Leu-61 to Ala-66.

The tissue distribution in T-cells, combined with the detected calcium flux activity in monocytes suggests that the protein product of this clone would be useful for the treatment and diagnosis of immune and hematopoietic disorders. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1217 of SEQ ID NO:63, b is an integer of 15 to 1231, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 54**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DHWPAGFLPPAPGLKFPVALEVFRKVLPAVCPTDCSGS AGKERN (SEQ ID NO:271). Polynucleotides encoding these polypeptides are also encompassed by the invention.

20 It has been discovered that this gene is expressed primarily in liver.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: metabolic diseases and liver conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., hepatic, liver, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder,

relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 161 as residues: Ser-31 to Gln-41.

5           The tissue distribution in liver suggests that the protein product of this clone would be useful for treatment and diagnosis of disorders of the metabolic system and liver disorders. Moreover, the protein product of this clone is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of  
10   hepatocyte progenitor cells). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
15   related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
20   general formula of a-b, where a is any integer between 1 to 598 of SEQ ID NO:64, b is an integer of 15 to 612, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

## 25   **FEATURES OF PROTEIN ENCODED BY GENE NO: 55**

When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates sensory neuron cells, and to a lesser extent in other neural cells and tissues, through the EGR1 signal transduction  
30   pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes



containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

It has been discovered that this gene is expressed primarily in T-cells and monocytes, and to a lesser extent in cancerous tissues, including cancerous colon  
5 tissue and placenta.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and haemopoietic disorders and cancer such as colon cancer, but also such cancers as breast cancer,  
10 cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, adenoma, and the like. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell  
15 type(s). For a number of disorders of the above tissues or cells, particularly of the immune and haemopoietic systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having  
20 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 162 as residues: Glu-63 to Trp-72.

The tissue distribution in T-cells and monocytes, combined with the detected  
25 EGR1 biological activity suggests that the protein product of this clone would be useful for treatment and diagnosis of disorders of the immune and haemopoietic systems and colon and other cancers. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

30 Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an

agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to  
5 transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the  
10 differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression cellular sources marked by proliferating cells suggests this protein may play a role in the  
15 regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell  
20 death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate  
25 apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
5 general formula of a-b, where a is any integer between 1 to 2256 of SEQ ID NO:65, b is an integer of 15 to 2270, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 56

The translation product of this gene has homology with several human keratin genes at the nucleotide level (see, for example, Troyanovsky, et al., Eur. J. Cell Biol. 59:127-137 (1992) which is hereby incorporated by reference herein). Based on the  
15 sequence similarity, the translation product of this clone is expected to share biological activities with keratin and growth factor proteins. Such activities are known in the art, and some of which are described elsewhere herein.

It has been discovered that this gene is expressed primarily in neutrophils.

Therefore, nucleic acids of the invention are useful as reagents for differential  
20 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and haemopoietic disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
25 the immune and haemopoietic system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

30 The tissue distribution in neutrophils suggests that the protein product of this clone would be useful for treatment and diagnosis of disorders of the immune and

haemopoietic system. Furthermore, sequence homology of the polynucleotides and polypeptides of the present invention with a number of human cytokeratin molecules, such as CK-8, CK-15, and CK-17, indicate that molecules of the present invention can be used diagnostically as markers of basal cell differentiation in complex epithelia and therefore indicative of a certain type of epithelial stem cells, as well as markers of the differentiation of other cell types such as neutrophils or other immune cells. Molecules of the present invention, or agonists or antagonists thereof, can also be used therapeutically to treat differentiation disorders of epithelial, neutrophil or other immune cell differentiation or activation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:66, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 57**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: EEIATSIEPIRDFLAIVFFASIGLHVFPPTFVAYELTVLVF LTLSVVV (SEQ ID NO:272). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in synovium, placenta, and stromal cells, and to a lesser extent in several other tissues and organs,

including, among others, bone marrow, palate, pituitary gland, and in tissue derived from osteosarcoma and chondrosarcoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: developmental disorders, as well as disorders of the musculoskeletal and haematopoietic systems, and cancers including especially osteosarcoma and chondrosarcoma, but also other cancers including breast cancer, colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer,  
10 stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, adenoma, and the like. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemopoietic and musculoskeletal  
15 systems, as well as developmental disorders, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., synovium, placenta, stromal, immune, hematopoietic, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
20 expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 164 as residues: Pro-81 to Ser-88.

The tissue distribution in placenta suggests that the protein product of this  
25 clone would be useful for treatment and diagnosis of developmental disorders. Polynucleotides and polypeptides of the present invention can be used diagnostically and therapeutically to detect and treat many cancers, particularly osteosarcoma and chondrosarcoma. In addition, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the  
30 skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chrondomalacia and

inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial  
5 osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid).

Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Protein,  
10 as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of  
15 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1249 of SEQ ID NO:67, b  
20 is an integer of 15 to 1263, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 58**

25 Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of renal mesangial cells to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of renal and developing cells and tissues. Thus,  
30 polynucleotides and polypeptides have uses which include, but are not limited to, activating renal and developing cells and tissues.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: YCNLQCR (SEQ ID NO:273). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in the whole  
5 developing embryo, as well as in ovarian cancer and placenta.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental or reproductive diseases and/or disorders, in addition to the following and ovarian cancer, as well as  
10 other cancers including breast cancer, colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, and the like. Similarly, polypeptides and antibodies directed to those polypeptides are useful to  
15 provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing and fetal system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph,  
20 amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in embryonic and ovarian tissue, combined with the detected calcium flux activity, suggests that the protein product of this clone would be  
25 useful for treatment and diagnosis of developmental disorders as well as ovarian and other cancers. Expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving  
30 cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of

some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Therefore, the polynucleotides and polypeptides of the present invention are  
5 useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.  
Alternatively, the protein is useful in the detection, treatment, and/or prevention of  
10 vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
20 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1603 of SEQ ID NO:68, b is an integer of 15 to 1617, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 59**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SALIGNPKGCGFCFSPVVLREWSVESWKSRLRPFQAICK  
LKTNFR (SEQ ID NO:274). Polynucleotides encoding these polypeptides are also  
30 encompassed by the invention.



It has been discovered that this gene is expressed primarily in hypothalamus and anergic T cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: neurological and inflammatory defects, diseases, and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of  
10 this gene at significantly higher or lower levels may be detected in certain tissues (e.g., neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 166 as residues: His-33 to Trp-38.

The tissue distribution in hypothalamus and T-cells suggests that the protein product of this clone would be useful for study and treatment of immune and nervous system disorders. The protein product of this clone is useful for the detection,  
20 treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction,  
25 aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role  
30 in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal

differentiation or survival. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1375 of SEQ ID NO:69, b

is an integer of 15 to 1389, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 60

The translation product of this gene shares nucleotide sequence homology with the human PKD1 gene which is thought to be important in polycystic kidney disease.

10 This gene is expressed widely with a predominant expression exhibited in liver, pediatric kidney, and in the whole 8 week old developing human embryo.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: cancer, growth, renal, and metabolic defects, diseases, and/or disorders. Similarly, polypeptides and antibodies  
15 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine, digestive and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., renal, metabolic, hepatic, developmental,  
20 and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in pediatric kidney suggests that the protein product of  
25 this clone would be useful for study and treatment of renal and general neoplasias and growth and development disorders. The protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and  
30 kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome.

Moreover, the expression within embryonic tissue suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders, particularly of the liver and other organs. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1882 of SEQ ID NO:70, b is an integer of 15 to 1896, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HEAALRGP (SEQ ID NO:275). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human striatum depression.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: stroke, in addition to other, neurologically-related diseases and/or defects. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of  
10 this gene at significantly higher or lower levels may be detected in certain tissues (e.g., neural, musculoskeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 168 as residues: Glu-50 to Glu-61.

The tissue distribution in human striatum depression suggests that the protein product of this clone would be useful for study and treatment of central nervous system disorders, such as seizures and other neurological conditions. The protein product  
20 of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal  
25 cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role  
30 in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal

differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
10 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 294 of SEQ ID NO:71, b is an integer of 15 to 308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 62**

This clone has homology to a cystine rich granulin peptide(s) from leucocyte(s) which has been termed Granulin E. Granulins inhibit keratinocytes and is useful topically for wound healing. The gene encoding the disclosed cDNA is  
20 believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

It has been discovered that this gene is expressed primarily in infant brain.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
25 diagnosis of the following diseases and conditions: neurological, developmental, and growth defects. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetus and the nervous system, expression of this gene at  
30 significantly higher or lower levels may be detected in certain tissues (e.g., neural, developmental, growth, and cancerous and wounded tissues) or bodily fluids (e.g.,

lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Based on the strong conservation of cysteine residues, the polypeptide of the present invention can be used to inhibit keratinocytes and promote wound healing.

The tissue distribution in infant brain suggests that the protein product of this clone would be useful for study and treatment of nervous system, neurodegenerative and developmental disorders. The protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The homology to granulin proteins suggest the protein product of this clone is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus),

keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athletes foot, and ringworm). Moreover, the protein product of this clone may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1674 of SEQ ID NO:72, b is an integer of 15 to 1688, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 63**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SNAAGNVVRAFLYINHLKL GCKVGLA (SEQ ID NO:276). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in prostate cancer and dendritic cells.



Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: reproductive, immune, and hematopoietic diseases, defects and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 170 as residues: Trp-47 to Thr-54.

The tissue distribution in prostate cells and tissues indicates that the protein products of this clone are useful for study, diagnosis and treatment of neoplasias, esp. of the prostate, and hormonal and metabolic disorders. Moreover, the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1124 of SEQ ID NO:73, b is an integer of 15 to 1138, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 64**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: NWAVLNMLLSKKGKITIFLGPLECGS (SEQ ID NO:277). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in B cell lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and hematopoietic diseases, disorders, and/or defects, particularly cancers. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hemopoietic and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in B cell lymphoma suggests that the protein product of this clone would be useful for study and treatment of blood and immune disorders and neoplasias, esp. of the lymphatic system. The protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 763 of SEQ ID NO:74, b is an integer of 15 to 777, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 65**

It has been discovered that this gene is expressed primarily in B cell lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and hematopoietic diseases, disorders, and/or defects, particularly cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hemopoietic and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in B cell lymphoma suggests that the protein product of this clone would be useful for study and treatment of neplasias, esp. of lymphatic organs, and immune disorders. The protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
 5 general formula of a-b, where a is any integer between 1 to 1046 of SEQ ID NO:75, b is an integer of 15 to 1060, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

#### 10. FEATURES OF PROTEIN ENCODED BY GENE NO: 66

The translation product of this gene shares sequence homology with a rat protein phosphatase, in addition to, a human heterogeneous nuclear ribonucleoprotein R (See Genbank Accession No.gil2697103 (AF000364)). When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1  
 15 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates sensory neuron cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. This gene also showed activity in  
 20 sensory neurons using the EGR assay described in the Example section.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PSHQTRKGKSAKLLDRPPEALRMKIITTTLLACHLQLEV  
 G V V V G G E V D ( S E Q I D N O:278),  
 FQASSANNQQNWGSQPIAQQPLQQGGDYSG  
 25 NYGYNNDNQEFYQDTYGQQWK (SEQ ID NO:279), WXPLLXTSGSPGLXGFG  
 TRMNGKEIEGEEIEIVLAKPPDKKRKERQAARQASRSTAYEDYYYHPPPRMPP  
 PIRGRGRGGGRGGYGYPPDYGYEDYYDDYYGYDYHDYRGGYEDPYYGYD  
 DGYAVRGRGGGRGGRGAPPPRGRGAPPPRGRAGYSQRGAPLGPPRGSRRG  
 RGGPAQQQRGRGSRGSRGNRGGNVGGKRKADGYNQPSKRRQPTTNRTGV  
 30 PNPSLSSRFSKVVTILVTMVTIMTTRNFIRILMGNSGSRQVRA (SEQ ID  
 NO:280), RMNGKEIEGEEIEIVLAKPPDKKRKER (SEQ ID NO:281), YYHPPP

RMPP PIRGRGRGGGRGGYG (SEQ ID NO:282), DYRGGYEDPYGYDDGYAV  
RGRGGGR (SEQ ID NO:283), PPPRGRAGYSQRGAPLGPPRGSRGGRGG (SEQ  
ID NO:284), and/or ADGYNQPDSK RRQPTTNRTGVPNPSLSSRFSKVVT (SEQ  
ID NO:285). Polynucleotides encoding these polypeptides are also encompassed by  
5 the invention. The gene encoding the disclosed cDNA is believed to reside on  
chromosome 1. Accordingly, polynucleotides related to this invention are useful as  
a marker in linkage analysis for chromosome 1.

It has been discovered that this gene is expressed primarily in human primary  
breast cancer, lung, and leukocytes.

10 Therefore, nucleic acids of the invention are useful as reagents for differential  
identification of the tissue(s) or cell type(s) present in a biological sample and for  
diagnosis of the following diseases and conditions: reproductive, immune, or  
pulmonary diseases and/or disorders, particularly breast cancer. Similarly,  
polypeptides and antibodies directed to those polypeptides are useful to provide  
15 immunological probes for differential identification of the tissue(s) or cell type(s). For  
a number of disorders of the above tissues or cells, particularly of the reproductive,  
immune and respiratory systems, expression of this gene at significantly higher or  
lower levels may be detected in certain tissues or cell types (e.g., reproductive,  
immune, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g.,  
20 lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual  
having such a disorder, relative to the standard gene expression level, i.e., the  
expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in breast cancer cells and tissues, in addition to immune  
cells, combined with the homology to a protein phosphatase suggests that the protein  
25 product of this clone would be useful for diagnosis and treatment of breast cancer and  
abnormalities of the lung and the immune system. Moreover, the expression of this  
gene product suggests a role in regulating the proliferation; survival; differentiation;  
and/or activation of hematopoietic cell lineages, including blood stem cells. This gene  
product may be involved in the regulation of cytokine production, antigen  
30 presentation, or other processes suggesting a usefulness in the treatment of cancer  
(e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein is useful in modulating the immune response to aberrant cells and cell types, particularly proliferative cells (e.g. protein may increase the immunogenicity of tumor antigens either directly or indirectly, or may activate apoptosis). The protein is useful in treating, detecting, and/or preventing various pulmonary disorders, which include, but are not limited to, ARDS, emphysema, and cystic fibrosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1489 of SEQ ID NO:76, b is an integer of 15 to 1503, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 67

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LQIPPSSQSLGLKNADSSI (SEQ ID NO:286), GGPPESAPW LPAVLRAPVLT SRCASSDSEGPVWFCQPGSGPSSTEMSCHCILGPGSSCLCVL RGSMTWTPSVPGWPQPAKETGASSCSVFSANNGSCPLPLHNHQRQASLDTGL SLEHVPGESYFYSPVG (SEQ ID NO:287), SSDSEGPVWFCQPGSGPSSTEMSC  
10 HCILGPGSSC (SEQ ID NO:288), WTPSVPGWPQPAKETGASSCSVFSANNG (SEQ ID NO:289), and/or QRQASLDTGL SLEHVPGESYF (SEQ ID NO:290).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human B cell lymphoma.

15 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune or hematopoietic diseases and/or disorders, particularly B cell lymphoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes  
20 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an  
25 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in B-cell lymphoma suggests that the protein product of this clone would be useful for diagnosis and treatment of immune or hematopoietic diseases and/or disorders, particularly proliferative conditions. Moreover, the  
30 expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including



blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene  
5 product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to  
10 transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other  
15 blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of  
20 neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as,  
25 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of  
30 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence

would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:77, b is an integer of 15 to 872, where both a and b correspond to the positions of  
5 nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 68**

In specific embodiments, polypeptides of the invention comprise the following  
10 amino acid sequence: SSSLVLTIRSQTLFLASFIHSTSIFCALN (SEQ ID NO:291). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in osteoarthritic cartilage.

Therefore, nucleic acids of the invention are useful as reagents for differential  
15 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: osteoarthritis and other bone/cartilage disorders, particularly degenerative conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of these tissue(s) or cell type(s). For a number of  
20 disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., skeletal, joint, autoimmune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression  
25 level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in osteoarthritic cartilage suggests that the protein product of this clone would be useful for the diagnosis, treatment, and/or prevention of osteoarthritis. Moreover, the gene product is useful in the detection and treatment  
30 of disorders and conditions affecting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma,

tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 559 of SEQ ID NO:78, b is an integer of 15 to 573, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 69**

The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

It has been discovered that this gene is expressed primarily in fetal brain, pharynx carcinoma, and Hodgkin's lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental and/or proliferative diseases and disorders, particularly pharynx carcinoma, and Hodgkin's lymphoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to

provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, proliferative cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 176 as residues: Tyr-30 to Ser-40.

The tissue distribution in pharynx carcinoma and Hodgkin's lymphoma suggests that the protein product of this clone would be useful for diagnosis and treatment of immune and proliferative conditions. Moreover, expression within fetal tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

Alternatively, the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia,

trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep  
5 patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein  
10 may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of  
15 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1495 of SEQ ID NO:79, b  
20 is an integer of 15 to 1509, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 70**

25 The translation product of this gene shares sequence homology with insulin-like growth factor binding protein. Moreover, the protein has homology to the human Slit-1 protein (See Genbank Accession No. gnlIPID1036170 (AB017167)), which is thought to play an integral role in neural development. In Drosophila embryogenesis, the slit gene has been shown to play a critical role in CNS midline formation. Each  
30 Slit gene encodes a putative secreted protein, which contains conserved protein-protein interaction domains including leucine-rich repeats (LRR) and epidermal

growth factor (EGF)-like motifs, like that of the *Drosophila* protein. The Slit genes form an evolutionary conserved group in vertebrates and invertebrates, and the mammalian Slit proteins may participate in the formation and maintenance of the nervous and endocrine systems by protein-protein interactions.

- 5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: the EGF-like domain: CCCRLGLSGPKC (SEQ ID NO:292); in addition to the following: RAFWGLGALQLLDLSANQLEAL (SEQ ID NO:293), HASGRRTGSADDGLQGRTGSGPPTAGAGGGGAAP (SEQ ID NO:294), VSAAAGARLAPRAPGAPAGCRPMRGCAARAAARKSLVPVLPAGWRS GPAA
- 10 AARPGPRRLAHAPSAARSRAGPGAVARPLPRRH LAAAHGRGCGPAAARAGA GSGPGARRAARVPTAGRPPGTHVHTSGQSGAPRDPEGEALADTWAQTGQGD SSSNSSSSGRGRDQEGPRMGAAPPPAPAVGGPLPVRPWSPSSAEPVLRPD AW ( S E Q I D N O : 2 9 5 ) , TRPAAERAPRTTGSRDAQAAGLPPRVPGAGGLPPCGALPGR
- 15 GLGRCCCCCCCCRLGLSGPKCRPGPRPRGPWAPRTAPRCARACREACQLSAL SLPAVPPGLSLRLRALLLDHNRVRALPPGAFAGAGALQRLDLRENGLHSVHV RAFWGLGALQLLDLSANQLEALAPGTFAPLRALRNLSLAGNRLARLEPAALG ALPLLRSLSLQDNELAALAPGLLGRLPALDALHLRGNPWGCGCALRPLCAWL RRHPLPASEAETVLCVWPGRLTLSPLTAFSDAAFSHCAQPLALRDLARGLHA
- 20 RAGLLPRQPGLPGAGLWAHRLPCAPPPPHRRPPPAETVQTRTPIPTPTAVPR P R T R G A P S A A A Q A ( S E Q I D N O : 2 9 6 ) , GCRPMRGCAARAAARKSLVPVLPAGWRS GP AAAARPGPRRLAHAPSA (SEQ ID NO:297), PGAVARPLPRRH LAAAHGRGCG PAAARAGA (SEQ ID NO:298), SGQSGAPRDPEGEALADTWAQTGQ (SEQ ID NO:299),
- 25 PPAPAVGGPLPVRPWSPSSAEPV (SEQ ID NO:300), APRTTGSRD AQAAGLPPRVPGAGGLP (SEQ ID NO:301), GPRPRGPWAPRTAPRCARACRE (SEQ ID NO:302), AVPPGLSLRLRALLLDHNRVRALPPGAFAGA (SEQ ID NO:303), LGALQLLDLSANQLEALAPGTFAP (SEQ ID NO:304), PPGAFAGAG ALQRLDLRENGLHSVHVRAFWGLGALQ (SEQ ID NO:305), RNLSLAGNRLA
- 30 RLEPAALGALPLLRSL (SEQ ID NO:306), LPALDALHLRGNPWGCGCALRP LCAW (SEQ ID NO:307), TVLCVWPGRLTLSPLTAFSDAAFSHCAQPLALRD

(SEQ ID NO:308), LHARAGLLPRQPGFLPGAGLWAHR (SEQ ID NO:309), and/or TVQTRTPIPTPTAVPRPRTRGAPS (SEQ ID NO:310). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 It has been discovered that this gene is expressed primarily in a breast cancer cell line, MDA36.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neural, reproductive, and proliferative diseases and/or disorders, particularly breast cancer and degenerative  
10 conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, reproductive, and  
15 proliferative cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
20 177 as residues: Met-1 to Arg-10, Arg-64 to Ala-71, Gly-124 to Gly-131, Pro-189 to Arg-194, Val-223 to Gly-228.

The tissue distribution in a breast cancer cells and tissues and homology to insulin-like growth factor binding protien suggests that the protein product of this clone would be useful for diagnosis and treatment of breast cancer, and other forms of  
25 cancer. Moreover, the homology to the conserved human slit-1 protein suggests that the protein is useful in the treatment, diagnosis, and/or prevention of neural disorders, particularly developmental and degenerative conditions. Similarly, the protein is useful for the treatment and/or diagnosis of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to  
30 Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia,

trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1095 of SEQ ID NO:80, b is an integer of 15 to 1109, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 71**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASGRPDRSSAPIGNSGLPCPDLEPLGGLQSKCRLCAPTEARGLWSRSLCSDRCTWRS (SEQ ID NO:311), and/or GLPCPDLEPLGGLQSKCRLCAPTEARGLW (SEQ ID NO:312). Polynucleotides encoding these polypeptides are also encompassed by the invention. This gene also maps to chromosome 1, and therefore can be used in linkage analysis as a marker for chromosome 1.



It has been discovered that this gene is expressed primarily in salivary gland and colon carcinoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: colon carcinoma and other digestive system or gastrointestinal diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression  
10 of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., digestive system, gastrointestinal, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, chyme, bile, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy  
15 tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 178 as residues: Val-34 to Leu-39, Ser-64 to Cys-74, Ser-86 to Ser-95, Arg-128 to Ala-136.

The tissue distribution in salivary gland and colon carcinoma suggests that the  
20 protein product of this clone would be useful for the treatment and diagnosis colon cancer and other digestive system diseases and/or disorders, such as ulcers, and other proliferative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
30 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 793 of SEQ ID NO:81, b is an integer of 15 to 807, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 72

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: QEWESELGERRKPLQA (SEQ ID NO:313). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 It has been discovered that this gene is expressed primarily in 6 week old human embryos.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: embryological defects; aberrant  
15 development; aberrant cellular proliferation (e.g. cancers), and other developmentally related or proliferative diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing human embryo, expression  
20 of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not  
25 having the disorder.

The tissue distribution in 6 week old human embryos suggests that the protein product of this clone would be useful for the diagnosis and/or treatment of defects in embryonic development. Elevated expression of this gene product in early 6 week human embryos suggests that this gene product plays a critical role in normal human  
30 development. Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant

Expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Moreover, this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1029 of SEQ ID NO:82, b is an integer of 15 to 1043, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 73

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: CQSSNLIFFQFVNILFNLMMDILVDFSITKMPINSIFSLYF

CYEII (SEQ ID NO:314). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in 6 week old human embryo.

5           Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: abnormal embryonic development; abnormal cellular proliferation; developmental defects, and other developmentally related or proliferative diseases and/or conditions. Similarly,  
10 polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing human embryo, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, and cancerous and  
15 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

          The tissue distribution in 6 week old human embryo suggests that the protein  
20 product of this clone would be useful for the diagnosis and treatment of disorders of human embryonic development. Expression of this clone in developing embryos suggests that it plays a critical role in early human development. Alternatively, it may be involved in key cellular proliferation events that occur during embryogenesis. Therefore misexpression of this gene in adult tissues may lead to abnormal patterns of  
25 cellular proliferation and cancer. Moreover, expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.  
30 Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell

death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1159 of SEQ ID NO:83, b is an integer of 15 to 1173, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 74

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GPVWLFCLTLCKPSQLFSQENSCMDVAGGVTTCLPP WFSRGAPAQMSQWPPSSDHGAVRAGRDSRVGPVQPSHLTCEGGKEEREKNK KAEVNPPTGMGLANRIPRDDITLKLNRNQGKLRTKENRTQSAKRHP (SEQ ID NO:315), VACKPENRTKTHFASSPACDGHALGGQVGFAICFLSCLFPPM (SEQ ID NO:316), and/or SHPMPNTPQKQLLFSEDNELLVSLRTGRKPTLQAALRVTG (SEQ ID NO:317). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in pleural cancer and endometrial tumors, and, to a lesser extent, in bone marrow & apoptotic T cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: pleural cancer; endometrial tumors; hematopoietic disorders; immune dysfunction. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lungs and immune system, expression  
10 of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not  
15 having the disorder.

The tissue distribution in pleural cancer and endometrial tumors indicates that the protein products of this clone are useful for the diagnosis and treatment of various reproductive cancers, including pleural cancer and endometrial tumors. In addition,

Expression of this gene product within T cells & bone marrow suggests that it  
20 may play a role in normal hematopoiesis. Therefore, this gene product may also be useful in the diagnosis and/or treatment of a variety of hematopoietic disorders, including defects in immune surveillance, inflammation, impaired immune function, and T cell lymphomas. Use of this gene product may be appropriate in situations designed to affect the proliferation, survival, and/or differentiation of various  
25 hematopoietic cell lineages, including blood stem cells.

Moreover, this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can  
30 result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in

acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein  
 5 may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
 10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
 15 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1547 of SEQ ID NO:84, b is an integer of 15 to 1561, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.

20

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 75

The translation product of this gene shares low sequence homology with dreg-2, a gene product originally identified in *Drosophila* that shows an oscillating pattern of expression tied into a circadian clock rhythm.

25 In specific embodiments, polypeptides of the invention comprise the following

a m i n o a c i d s e q u e n c e :

AHRLQIRLLTWDVKDTLLRLRHPLGEAYATKARAHGLEV

EPSALEQGGFRQAYRAQSHSFPNYGLSHGLTSRQWWLDVVLQTFHLAGVQDA

QAVAPIAEQLYKDFSHPCWTQVLDGAEDTLRECRTRGLRLAVISNFDRRLEGI

30 LXGLGLREHFDFVLTSEAAGWPKPDPRIFQEALRLAHMEPVVAAHVGDNLYL

CDYQGPRAVGMHSFLVVGPPALDPVVRDSVPKEHILPSLAHLLPALDCLEGS

T P G L ( S E Q I D N O:319),  
 EGDPRGRPRRPLGPPPQLTLPTALXDILRQVRAPGLRLSRA  
 LEVGRKGSPIFKIQIYL (SEQ ID NO:318), IRLLTWDVKDTLLRLRHPLGEAYA  
 TKA (SEQ ID NO:320), LEQGFRQAYRAQSHSFPNYGLSHG (SEQ ID NO:321),  
 5 HLAGVQDAQAVAPIAEQLYKDFSHPC (SEQ ID NO:322), VLDGAEDTLRECR  
 TRGLRLAVIS (SEQ ID NO:323), REHFDFVLTSEAAGWPKPDPRIFQEA (SEQ  
 ID NO:324), EPVVAAHVGDNYLCDYQGPRAVGMHSFL (SEQ ID NO:325),  
 and/or VVRDSVPKEHILPSLAHLLPALD (SEQ ID NO:326). Polynucleotides  
 encoding these polypeptides are also encompassed by the invention.

10 It has been discovered that this gene is expressed primarily in tumors of the  
 pancreas & thymus and to a lesser extent in a variety of fetal tissues, including fetal  
 brain, liver, spleen, and kidney.

Therefore, nucleic acids of the invention are useful as reagents for differential  
 identification of the tissue(s) or cell type(s) present in a biological sample and for  
 15 diagnosis of the following diseases and conditions: pancreatic cancer; thymic cancer;  
 disorders of fetal development; abnormal cellular proliferation; hematopoietic  
 disorders. Similarly, polypeptides and antibodies directed to those polypeptides are  
 useful to provide immunological probes for differential identification of the tissue(s)  
 or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
 20 the pancreas and immune system, expression of this gene at significantly higher or  
 lower levels may be detected in certain tissues or cell types (e.g., developmental,  
 metabolic, immune, hematopoietic, and cancerous and wounded tissues) or bodily  
 fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid or spinal fluid)  
 taken from an individual having such a disorder, relative to the standard gene  
 25 expression level, i.e., the expression level in healthy tissue from an individual not  
 having the disorder.

The tissue distribution in proliferative and developmental cells and tissues  
 indicates that the protein products of this clone are useful for the diagnosis and  
 treatment of cancers, particularly pancreatic and thymic cancer. Expression of this  
 30 gene product within various fetal tissues also indicates that it is useful in the diagnosis  
 and/or treatment of human developmental disorders. Taken together, the observation



that this gene product is expressed in cancers and in fetal tissues indicates that it plays a role in proliferation and/or differentiation events that are associated with early development. Misexpression of this gene product in adult tissues, therefore, may directly contribute to abnormal cellular proliferation and/or dedifferentiation that  
5 accompanies cancer. Finally,

Moreover, the expression of this gene product in fetal liver/spleen also suggests that it plays a role in hematopoiesis, and is useful in the diagnosis and/or treatment of a variety of disorders of the immune system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or  
10 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
15 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1419 of SEQ ID NO:85, b is an integer of 15 to 1433, where both a and b correspond to the positions of  
20 nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 76**

In specific embodiments, polypeptides of the invention comprise the following  
25 amino acid sequence: IRKLGPGGLAPCSCRSQVFPRV (SEQ ID NO:327).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in frontal cortex, particularly derived from epileptic patients.

Therefore, nucleic acids of the invention are useful as reagents for differential  
30 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: epilepsy; neurodegenerative

diseases and disorders, particularly learning disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS, and/or PNS, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in frontal cortex tissue suggests that the protein product of this clone would be useful for the diagnosis and/or treatment of disorders of the brain and nervous system, particularly epilepsy. Moreover, the expression of this gene product suggests that it may play a role in various critical processes of the nervous system, including nerve survival, pathfinding, signal conductance, and/or synapse formation. It may have effects on various processes including homeostasis, learning, motor function, language, etc. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1363 of SEQ ID NO:86, b is an integer of 15 to 1377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 77**

In specific embodiments, polypeptides of the invention comprise the following

a m i n o a c i d s e q u e n c e :

- 5 KPLRMARPGGPEHNEYALVSAWHSSGSYLDSEGLRHQDD  
 FDVSLLVCHCAAPFEEQGEAERHVLRLQFFVVLTSQRELFPRLTADMRRFRK  
 PPRLPPEPEAPGSSAGSPGEASGLILAPGPAPLFPPLAAEVGMARARLAQLVRL  
 AGGHCRDRTLWKRLFLLEPPGPDRRLRLGGRLALAELEELLEAVHAKSIGDIDP  
 QLDCFLSMTVSWYQSLIKVLLSRFPRAVAISKAQTWELSTWLR (SEQ ID  
 10 NO:328), ARGTLELPTPLIAAHQLYNYVADHASSYHM (SEQ ID NO:329),  
 SHCEWPGQG AQNTTSMPWCRHGTVLAPTWTLRDFDTR (SEQ ID NO:330),  
 PLTTVSHLCPL  
 SLRVFTSHLDITAGHSHRDDTWVPIPALPLKHLRPPSSPFALGPWVSHPLMRW  
 VQKLSHLHSNPGTGFSMGGKSAEKLKC (SEQ ID NO:331), STAARGAPGPGR  
 15 AGGTPRSSPCQIHWGHRPPAGLLPIHDGLLVPEPDQSSPKPLPQSCRHFQSPDL  
 GTQYLVALNQKFTDCSALVFWTPLRKDVSEVVFREALPVQPQDTRSPPAQLV  
 STYHHLESVINTACFTLLDPPPLKGVDTTECHCSLNHGPTRLPARGRTDQPF  
 W A P G Q A R H ( S E Q I D N O : 3 3 2 ) ,  
 HQRLCNYVLRVCCPSLAAGTALPKHPQPLTHPGL  
 20 QRVRSTPRTPWALLGYSFRRPW (SEQ ID NO:333),  
 PGGPEHNEYALVSAWHSS GSYLDSEGLR (SEQ ID NO:334),  
 DVSLLVCHCAAPFEEQGEAERHVLRL (SEQ ID NO:335),  
 RLTADMRRFRKPPRLPPEPEAPGSSAGS (SEQ ID NO:336), GEASGLI  
 LAPGPAPLFPPLAAEVGM (SEQ ID NO:337),  
 25 TLWKRLFLLEPPGPDRRLRLGGRL (SEQ ID NO:338), and/or  
 LAELEELLEAVHAKSIGDIDPQLDCFLS (SEQ ID NO:339). Polynucleotides  
 encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in fetal liver/spleen and leukocytes, and to a lesser extent in a colon adenocarcinoma cell line.

- 30 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for

diagnosis of the following diseases and conditions: hematopoietic disorders; immune dysfunction; colon cancer; colorectal adenocarcinoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
5 of the above tissues or cells, particularly of the immune system and colon, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., hematopoietic, immune, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard  
10 gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 184 as residues: Leu-16 to Ser-23, Ser-38 to Pro-43, Gly-53 to Leu-60.

The tissue distribution in colon adenocarcinoma suggests that the protein  
15 product of this clone would be useful for the diagnosis and/or treatment of gastrointestinal diseases and/or disorders, particularly proliferative conditions. Expression of this gene product in fetal and proliferative cells and tissues suggests that it may be a marker cancers, and that its misregulated expression may in fact contribute to the development or progression of the types of cancers dictated by its  
20 expression.

Similarly, the expression of this gene product in fetal liver/spleen - a primary site of early hematopoiesis - taken together with its expression in peripheral blood leukocytes suggests that this gene product may play a role in a variety of hematopoietic processes, including the survival, proliferation, activation, and/or  
25 differentiation of all blood cell lineages, including the totipotent hematopoietic stem cell. Such a gene product may therefore play a role in a variety of hematopoietic disorders including inflammation; immune dysfunction; defects in immune surveillance; and hematopoietic cancers and lymphomas. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern  
30 formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1701 of SEQ ID NO:87, b is an integer of 15 to 1715, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 78**

The gene encoding the disclosed cDNA is believed to reside on chromosome 20. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 20.

It has been discovered that this gene is expressed primarily in brain.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s)

or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. This gene is believed to reside on chromosome 20, D20S111-D20S195. Polynucleotides corresponding to this gene are useful, therefore, as chromosome markers.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 185 as residues: Met-1 to Tyr-6, Thr-38 to Ala-44.

The tissue distribution in brain tissue indicates that the protein products of this clone are useful for diagnosis and treatment of disorders of the central nervous system. Moreover, the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

In addition, elevated expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention

5 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 403 of SEQ ID NO:88, b is an integer of 15 to 417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

10

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 79

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent,

15 other immune and hematopoietic cells or cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS

20 element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: FQLYFNPELIFKHFQIWRLITNFLFFGPGVGFNFLNMFILY

RYCRMLEEGSFRGRTADFVFMFLFGGFLMTLFGFLVSLVFLGQAFTIMLVYV

25 WSRXNPYVRMNFGLLNQAPFLPWVLMGFSLLLGNSIIVDLLGIAVGHYFF

LEDVFPNQPGGIRILKTPSILKAIFDTPDEDPNYNPLPEERPGGFAWGEGQ SEQ

I D N O : 3 4 0 ) ,

GVGQATVGKMAYQSLRLEYLQIPPVSRAYTTACVLTTAAVQLELITPF

QLYFNPELIFKHFQIWRLITNFLFFGPGVGFNFLNMFILYRYCRMLEEGSFRGR

30 TADFVF (SEQ ID NO:341), LIFKHFQIWRLITNFLFFGPGVGF (SEQ ID NO:342),

FLYRYCRMLEEGSFRGRTADFVFMF (SEQ ID NO:343), LVFLGQAFTIMLVYV

WSRXNPYV (SEQ ID NO:344), VLMGFSLLLGNSIIVDLLGIA (SEQ ID NO:345), NQPGGIRILKTPSILKAIFDTPDED (SEQ ID NO:346), RLEYLQIPPVSRAYTTAC VLTAAVQLE (SEQ ID NO:347), and/or RLITNFLFFGPVGFNLFNMIFLYRYC RMLE (SEQ ID NO:348). Polynucleotides encoding these polypeptides are also  
5 encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

It has been discovered that this gene is expressed primarily in smooth muscle, fetal brain, fetal liver and to a lesser extent in activated macrophage, colon cancer.

10 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental diseases, immune-related diseases, neural disorders, and vascular diseases and conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide  
15 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, vascular, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,  
20 plasma, amniotic fluid, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in fetal liver, macrophage, and fetal brain indicates that the protein products of this clone are useful for treating and diagnosis of immune  
25 system-related diseases and CNS diseases. Moreover, the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow  
30 reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as



infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism.

Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells, combined with the GAS biological activity, suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention

are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1153 of SEQ ID NO:89, b is an integer of 15 to 1167, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 80

The translation product of this gene shares sequence homology with proacrosin binding proteins (sp32) from non-human mammalian species. The binding of sp32 to proacrosin may be involved in packaging the acrosin zymogen into the acrosomal matrix. See, for example, J Biol Chem. 1994 Apr 1; 269(13): 10133-10140, incorporated herein by reference. Accordingly, the inventors have termed the translation product of this gene human sp32 or "h-sp32". Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of PMN to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both neutrophils, and to a lesser extent in other immune and hematopoietic cells. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASAGPDGSSPA (SEQ ID NO:349), ELLLEKPKPWQPPAAAPHRALLVLCYSIVENTCIITPTAKAWKYMEEEILGFG KSVCDLGRHRMSTCALCDFCSLKLEQCHSEASLQRQQCDTSHKTPFAAPCL P P R A C P S A T R ( S E Q I D N O : 3 5 0 ) , LPGWGFPTKICD TDYIQYPNYCSFKSQCLMR NNRKVSRRMRLQNETYSALSPGKSEDVVLRWSEQFSTLTGQFG (SEQ ID NO:351), SPVLLPAFPPLPVPLLALPVSAPLPACVLVSAPACAPLLAPACAL ALAPGFPGTRRIVGALPRCC (SEQ ID NO:352), LLVLCYSIVENTCIITPTAK AWKYMEEEILGFGKS (SEQ ID NO:353), and/or LKLEQCHSEASLQRQQC DTSHKTPFA (SEQ ID NO:354). Polynucleotides encoding these polypeptides are

also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

It has been discovered that this gene is expressed primarily in testis.

5 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For  
10 a number of disorders of the above tissues or cells, particularly of the reproductive diseases, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, testis, prostate, epididymus, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having  
15 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. This gene is believed to map to chromosome 12 and is thought to be useful as a chromosome marker.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
20 187 as residues: Asp-27 to Ser-32, Pro-52 to Thr-58, Arg-63 to Asn-70, Gln-78 to Gly-83, Thr-107 to Asn-113, Thr-160 to Val-176, Ser-188 to Gly-241, Leu-248 to Pro-265, Tyr-302 to Gly-314.

The tissue distribution in testis, combined with the specific homology to the sp32 protein indicates that the protein products of this clone are useful for the  
25 diagnosis, treating, and/or prevention of reproductive diseases and/or disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is  
30 also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents.

Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. The protein is useful in application and utility as a contraceptive, either directly or indirectly. Based upon the detected calcium flux activity, the protein may also be useful as an effect treatment for infertility (i.e. for inhibiting autoimmune disorders). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1878 of SEQ ID NO:90, b is an integer of 15 to 1892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 81**

The translation product of this contig has consistent sequence homology with a number of previously described viral tat proteins (see, for example, Stevens, et al., J. Virol. 64:3716-3725 (1990), which is hereby incorporated by reference, herein).

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: QVSGILSLSCGMDGLALDGSPSPSPXTEKAGRCISQTSL (SEQ ID NO:355), QVSGILSLSCGMDGLALDGSPSPSPXTEKAGRCISQTSLP GKWEV (SEQ ID NO:356), RASKTVPRMPPNWPAPKMPCLCHIRTV EHLGTIS

SGAPGRPTGQQAARTYHICWIHPGQKIDSLPPSSQHPRSQQ LAPGTWPSTSTT  
 KPAEETLGSSASLPISQARKSEKCTFQPSWPXVRGKESHQVPAHPSHRTETES  
 D HSPVRKPPSRGTRTGDFTVGDWSEAWLLELALL (SEQ ID NO:357), RMPPN  
 WPAKMPCLCHIRTVEHLG (SEQ ID NO:358), GRPTGQQAARTYHICWIHPG  
 5 QKIDS (SEQ ID NO:359), WPSTSTTKPAEETLGSSASLPISQA (SEQ ID NO:360),  
 KSEKCTFQPSWPXVRGKESHQVP (SEQ ID NO:361), and/or KPPSRGTRTGDFTVGDWSEAWLLE (SEQ ID NO:362). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed almost exclusively in  
 10 neutrophils.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential  
 15 identification of the tissue(s) or cell type(s). For a number of disorders of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard  
 20 gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. In addition, molecules of the present invention can be used to regulate transcription and translation of genes in cells of the immune system, as well as in other cell types. Such transcriptional and translation regulation is useful for diagnosing and treating a number of disorders in which an altered state of  
 25 transcription and translation may be a factor in the disorder. Such disorders include many viral infections, particularly of immune cells, including HIV-1, HIV-2, human T-cell lymphotropic virus (HTLV)-I, and HTLV-II, as well as other DNA and RNA viruses such as herpes simplex virus (HSV)-1, HSV-2, HSV-6, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes samirii, adenoviruses, rhinoviruses,  
 30 influenza viruses, reoviruses, and the like. In addition, the ability to use molecules of the present invention to molecularly regulate the processes of transcription and

translation is useful in the diagnosis and treatment of many types of cancers, particularly those of the immune system, including ovarian cancer, breast cancer, colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, and the like.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 188 as residues: Gln-2 to Trp-12, Ala-30 to Glu-35, Gln-42 to Ser-51.

The tissue distribution in neutrophils, combined with the homology to viral tat proteins suggests that the protein product of this clone is useful for the diagnosis and treatment of immune disorders, particularly viral infections and proliferative disorders. Further, since this clone has a high degree of sequence relatedness to factors which are involved in the regulation of transcription and translation, this clone is useful as a regulator of such processes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 509 of SEQ ID NO:91, b is an integer of 15 to 523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 82

The translation product of this contig has clear sequence identity with a number of thioredoxins and endoplasmic reticulum resident proteins (see, for

example, Shorrosh and Dixon, Plant J. 2:51-58 (1992), which is hereby incorporated by reference, herein).

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PCADCLSAWA (SEQ ID NO:363). Polynucleotides encoding  
5 these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

It has been discovered that this gene is expressed primarily in adipocytes and  
10 striatum depression, and in lower abundance in prostate, whole brain, fetal liver, and spleen.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: Prostate cancer, CNS diseases,  
15 immune disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, hematopoietic,  
20 immune, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Since the translation product of this clone has a high degree of sequence relatedness  
25 to many thioredoxins, it can be used as a food additive to improve flour quality or to suppress the anti-nutritional effects of leguminous plants. Molecules of the present invention can further used to inactivate toxins, for example, bee or snake venom.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 189 as residues: Trp-43 to Ala-49, Pro-68 to Ala-74, Glu-100 to Gly-111, Glu-120 to  
30 Asn-125, Pro-141 to Ala-154, Asp-157 to Lys-171, Cys-177 to Ile-182, Ser-248 to Leu-253, Thr-280 to Glu-285, Gly-353 to Val-359.

The tissue distribution in whole brain suggests that the protein product of this clone would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, 5 Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including 10 disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The secreted protein can also be used to determine 15 biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating 20 human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); 25 hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies 30 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.



Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1368 of SEQ ID NO:92, b is an integer of 15 to 1382, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 83**

When tested against TF-1 cell lines, supernatants removed from cells containing this gene activated the ISRE (interferon-sensitive responsive element ) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, in immune and hematopoietic cells or tissues, through the JAK-STAT signal transduction pathway. ISRE is a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASGYLCIVLL (SEQ ID NO:364). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed exclusively in Rejected Kidney.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: kidney and other urinary tract

disorders and disorders related to, or resulting from, transplantation. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and renal systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., renal, kidney, urogenital, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Molecules of the present invention are particularly useful in the diagnosis and treatment of disorders related to transplantation, particularly kidney transplantation.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 190 as residues: Asn-49 to Gln-54, Glu-150 to Asp-159.

The tissue distribution in rejected kidney tissue suggests that the protein product of this clone would be useful for diagnosis and treatment of disorders related to or resulting from rejection of transplanted organs, particularly the kidney. Moreover, the protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Considering the tissue distribution and detected ISRE biological activity, the protein is useful in modulating the immune response to aberrant kidney proteins, including autoantigens and aberrant proteins which are often present in degenerative and proliferative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
5 general formula of a-b, where a is any integer between 1 to 1733 of SEQ ID NO:93, b is an integer of 15 to 1747, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

#### 10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 84**

The translation product of this gene shares sequence homology with the conserved MAL and plasmolipin protein (Magyar, et al, Gene 189:269-275 (1997); See Genbank Accession No.gnllPIDle183885), which are thought to be important in modulating T cell function, and proper CNS function, respectively. When tested  
15 against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, immune or hematopoietic cells and tissues, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT  
20 pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise the following  
25 amino acid sequence: NSARAARAEIVLGLLVWTLIAGTEYFRVPAFGWV (SEQ ID NO:365). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in T cells.

Therefore, nucleic acids of the invention are useful as reagents for differential  
30 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune, hematopoietic, and neural diseases and/or disorders. Similarly,

polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in

5 certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Nucleic acids of the present invention are useful as probes for

10 detecting traumatic and pathological changes in the central and peripheral nervous systems. Molecules of the present invention may be involved in regulating the growth of Schwann cells and other neural cells. Molecules of the present invention are also useful as modulators of the interaction between Schwann cells and other neural cells and the extracellular matrix and is therefore useful for the therapeutic intervention in

15 nerve damage primarily by facilitating regeneration of damaged axons and regenerating nerve cells in damaged nervous system tissues.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 191 as residues: Ser-58 to His-64.

The tissue distribution in T-cells, combined with the homology to the MAL

20 and plasmolipin proteins and the detected GAS biological activity suggests that the protein product of this clone would be useful for the diagnosis and treatment of immune disorders including, but not limited to, AIDS and other immunodeficiencies. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell

25 lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an

30 agent for immunological disorders including arthritis, asthma, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne,

neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus  
5 erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of  
10 various blood lineages, and in the differentiation and/or proliferation of various cell types.

The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a  
15 very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy);  
20 stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia; cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as  
25 antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 586 of SEQ ID NO:94, b is an integer of 15 to 600, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 85**

The translation product of this clone has sequence identity to a protein tyrosine kinase reported by Oates and Wilks (The Worm Breeders Gazette 14:87-87 (1995), which is hereby incorporated by reference herein). The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

It has been discovered that this gene is expressed primarily in cerebellum, adult brain, retina, spinal cord, and kidney cortex.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neural, visual, and renal diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, retina, and kidney cortex. Expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, visual, renal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in cerebellum, adult brain, and spinal cord tissue suggests that the protein product of this clone would be useful for the diagnosis and treatment of neural diseases and disorders. The protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 572 of SEQ ID NO:95, b

is an integer of 15 to 586, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 86

The translation product of this clone has homology to trkB, and it is thought that the protein of the present invention is a novel novel neural receptor protein-tyrosine kinase, a trkB homolog (See for example, ). This protein is likely to be derived from a gene for a ligand-regulated receptor closely related to the human trk  
10 oncogene. Northern (RNA) analysis showed that the trkB gene is expressed predominantly in the brain and that trkB expresses multiple mRNAs, ranging from 0.7 to 9 kb. Hybridization of cerebral mRNAs with a variety of probes indicates that there are mRNAs encoding truncated trkB receptors.

In specific embodiments, polypeptides of the invention comprise the sequence  
15 PCSPDPSPLPGAFVWRVLWVC (SEQ ID NO:366). Polynucleotides encoding this polypeptide are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in breast cancer, colon tumor, and B-cell lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential  
20 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: breast cancer, colon tumor, B-cell lymphoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
25 the immune, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, gastrointestinal, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy  
30 tissue from an individual not having the disorder.



Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 193 as residues: Ser-29 to Asn-40.

The tissue distribution in proliferative cells and tissues suggests that the protein product of this clone would be useful for the treatment, detection, and/or prevention of cancer, particularly in the indicated tissues. The expression within cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

Alternatively, the homology to the trkB protein suggests the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal

differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
10 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 788 of SEQ ID NO:96, b is an integer of 15 to 802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 87**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ARACFAYNGVCSEGRWCDSHFHGSV (SEQ ID NO:367), MSNMGKIPSLSLHIPINKYICSRIPKFIQKVNKSTVLQICLKRQIILNKNKMSDH  
20 SKIGKANLVQIDIHSLGIVETGCVPSKRYCTLLTEQSGFPFLSHP (SEQ ID NO:368), MAGCCLKLFGVLSLCFLCGLISIERVICNPVSADFQVSTFCQRHCLLR SKVMFXIKGXTATIEVINENCTLVAAPPIGFPIXFL (SEQ ID NO:369), MSDHS KIGKANLVQIDIHSLGIVETGCVPSKRYCTLLTEQSGFPFLSHP (SEQ ID  
25 NO:370), MAGCCLKLFGVLSLCFLCGLISIERVICNPVSADFQVSTFCQRHCL LRSK (SEQ ID NO:371), VMFXIKGXTATIEVINENCTLVAAPPIGFPIXFL (SEQ ID NO:372). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in dendritic cells,  
30 and smooth muscle.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune, hematopoietic, and vascular diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., immune, hematopoietic, smooth muscle vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 194 as residues: Asp-40 to Ser-52.

The tissue distribution in dendritic cells suggests that the protein product of this clone would be useful for immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1212 of SEQ ID NO:97, b is an integer of 15 to 1226, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 88**

The translation product of this gene shares sequence homology with androgen-dependant expressed protein from golden hamster hair follicles which is thought to be important in regulating the secretions from glands in the skin (See GenBank Accession No. gil191315).

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PTEGRQKVLKTFTVPRSALAMTKTSTCIYHFLVLSWYTF LNYYISQEGKDEVKPKILANGARWKY (SEQ ID NO:373), PTEGRQKVLKTF TVPRSALAMTKT (SEQ ID NO:375), PRSALAMTKTSTCIYHFLVLSWYTF LN YYISQEGK (SEQ ID NO:374), and/or FLNYYISQEGKDEVKPKILANGARWKY  
10 (SEQ ID NO:376). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in lung, colon cancer, and testis.

Therefore, nucleic acids of the invention are useful as reagents for differential  
15 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of secretory cells including cells in the lung, colon, testis and the skin. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
20 of the above tissues or cells, particularly of the secretory epithelial cells in the lung, intestine, testis and skin, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
25 the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 195 as residues: Val-21 to Asp-30, Pro-101 to Thr-109.

The tissue distribution and homology to androgen regulated protein suggests that the protein product of this clone would be useful for treating disorders that  
30 involve highly secretory cells including those in the colon, testis, and skin. It may be useful for diagnosing disorders such as colon, lung, or testicular cancer and may be

used to treat pulmonary conditions in patients with compromised respiratory function. In addition, the polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents.

Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1106 of SEQ ID NO:98, b is an integer of 15 to 1120, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 89**

The translation product of this gene shares sequence homology with dec-205 a transmembrane protein which is thought to be important in antigen presentation in dendritic cells and T-cells.

It has been discovered that this gene is expressed primarily in macrophage, dendritic cells, lung and ulcerative colitis.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: inflammatory diseases such as ulcerative colitis. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or  
10 lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 196 as residues: Asp-30 to Arg-36, Gln-59 to Val-65.

The distribution in macrophage, dendritic cells, lung and ulcerative colitis tissues, and homology to antigen presenting receptors suggests that the protein product of this clone would be useful for modulating the immune response in both  
20 acute and chronic inflammatory conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
30 general formula of a-b, where a is any integer between 1 to 2582 of SEQ ID NO:99, b is an integer of 15 to 2596, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 90**

5           This gene maps to chromosome 22 and therefore polynucleotides of the present invention can be used in linkage analysis as a marker for chromosome 22.

          In specific embodiments, polypeptides of the invention comprise the sequence FKDQLVYPLLAFT (SEQ ID NO:377) and/or RQALNLPDVFGGLV (SEQ ID NO:379). Polynucleotides encoding these polypeptides are also encompassed by the  
10   invention.

          It has been discovered that this gene is expressed primarily in fetal spleen and liver as well as cd34 positive cells and to a lesser extent in several tissues suggesting a presence in blood or blood forming tissues.

          Therefore, nucleic acids of the invention are useful as reagents for differential  
15   identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental defects in the blood and blood forming cells. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential  
20   identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., fetal spleen and liver as well as cd34 positive cells, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
25   expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

          Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 197 as residues: Gln-54 to Gly-61, Asn-79 to Leu-91, Glu-99 to Thr-105, Pro-120 to Gln-126, Pro-128 to Phe-134, Arg-150 to Arg-156, Arg-160 to Arg-170.

30           The tissue distribution in fetal spleen and liver as well as cd34 positive cells suggests that the protein product of this clone would be useful for treating disorders in

the development, proliferation, or regulation of blood forming cells including diseases such as lymphomas, granulomas, leukemias, and in the preservation and or replenishment of stem cells in the blood.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
10 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1006 of SEQ ID NO:100, b is an integer of 15 to 1020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 91**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ATASHDLLLF (SEQ ID NO:379), MSINICLMQSKTQGSCQ  
YLLPVPVPIILKVSTVFSLLSLFRLFLSFCPPHPKKCSYLLKYYGPLEGHKTLX  
20 YLRTNLGVIQPPLRMYYAAEDCNGIG (SEQ ID NO:380), MSINICLMQSKTQGS  
CQYLLPVPVPIILKVSTVFSLLSLFRLFL (SEQ ID NO:381), and/or  
SFCPPHPK KCSYLLKYYGPLEGHKTLXYLRTNLGVIQPPLRMYYAAEDCNGIG  
(SEQ ID NO:382). Polynucleotides encoding these polypeptides are also encompassed by the invention.

25

It has been discovered that this gene is expressed primarily in T cells, fetal heart and chronic lymphocytic leukemia and to a lesser extent in kidney, lung, and 16 week embryos.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
30 diagnosis of the following diseases and conditions: disorders of the blood including abnormalities in T cell function or blood cell proliferation such as leukemia .



Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be  
5 detected in certain tissues or cell types (e.g., T cells, fetal heart and chronic lymphocytic leukemia, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 198 as residues: Leu-45 to Val-50.

The tissue distribution in T cells, fetal heart and chronic lymphocytic leukemia suggests that the protein product of this clone would be useful for treating abnormalities of the blood particularly those involving T-cells and the abnormal  
15 proliferation of blood cells such as lymphocytic leukemia. In addition, it suggests the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be  
20 involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an  
25 agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host  
30 diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia,

rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed  
5 progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

The expression in fetal heart tissue would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. The tissue distribution in kidney  
10 suggests the protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe  
15 kidney, polycystic kidney, and Falconi's syndrome.

In addition, the tissue distribution in embryonic tissue suggests the protein product of this clone is useful for the diagnosis, detection, and/or treatment of developmental disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the  
20 regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell  
25 death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue  
30 differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1506 of SEQ ID NO:101, b is an integer of 15 to 1520, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 92

The translation product of this gene shares sequence homology with ctg4 which is a glutamine repeat containing gene thought to be a candidate genetic disease locus.

In specific embodiments, polypeptides of the invention comprise the sequence  
 20 KEEDDDTERLPSKCEVCKLLSTE (SEQ ID NO:383 and 384) LQAELSRTGRSR  
 EVLELGQ (SEQ ID NO:385 and 386), RQAVIVCRRRFV (SEQ ID NO:387),  
 PPRWAHPKAPEGSPDPPSPPSALGLSVLPWSDSDPWHISVSPCAQREHYSPGS  
 AHINSLRPLPALSLKRCKARVSSSCLYPAPAPAPAPLEIDRCDSVPPVALCSAA  
 YTLRICWASVLCHRPPPSTSQPKPRARPKKGKAIFPTAQVP (SEQ ID NO:388),  
 25 PPRWAHPKAPEGSPDPPSPPSALGLSVLPWSDSDPWHISVSPCAQREHYSPGS  
 AHINSLRPLPALSLKRCK (SEQ ID NO:389), and/or ARVSSSCLYPAPAPAPAPL  
 EIDRCDSVPPVALCSAA YTLRICWASVLCHRPPPSTSQPKPRARPKKGKAIFPT  
 AQVP (SEQ ID NO:390). Polynucleotides encoding these polypeptides are also encompassed by the invention.

30 It has been discovered that this gene is expressed in several tissues including lung, heart, kidney, adrenal gland, smooth muscle, cerebellum, and embryonic tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: inherited developmental disorders possibly with a neuropsychiatric component. Similarly, polypeptides and antibodies  
5 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma,  
10 urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 199 as residues: Lys-25 to Ser-36, Ser-53 to Glu-60, Thr-70 to Arg-75, Arg-111 to  
15 Thr-119, Glu-161 to Leu-189.

The tissue distribution and homology to glutamine repeat family member CTG4 suggests that the protein product of this clone would be useful for identifying and treating specific diseases related to nucleotide triplet expansion. The tissue distribution in embryonic tissue suggests the protein product of this clone is useful for  
20 the diagnosis, detection, and/or treatment of developmental disorders. The relatively specific expression of this gene product during embryogenesis suggests it may be a key player in the proliferation, maintenance, and/or differentiation of various cell types during development. It may also act as a morphogen to control cell and tissue type specification. Because of potential roles in proliferation and differentiation, this  
25 gene product may have applications in the adult for tissue regeneration and the treatment of cancers. Expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1292 of SEQ ID NO:102, b is an integer of 15 to 1306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 93**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: EEKLFTSAPGRDFWVMGETRDGNEEN (SEQ ID NO:391). Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

It has been discovered that this gene is expressed primarily in cancerous and fetal tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: cancer, developmental anomalies or fetal deficiencies. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system and developing fetus, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 200 as residues: Met-1 to Ser-6.

5       The tissue distribution in fetal tissue suggests that the protein product of this clone would be useful for the treatment and diagnosis of developmental anomalies or fetal deficiencies. In addition to fetal tissue, expression in a variety of cancerous tissues suggests a role in the treatment and diagnosis of uncontrolled cell proliferation and/or differentiation (e.g. cancer). Moreover, the expression within embryonic tissue  
10       and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders.

Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can  
15       result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders  
20       and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25       Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
30       would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:103, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 94**

The gene encoding the disclosed cDNA is believed to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

10 This gene is expressed primarily in hypothalamus, T-cells, and adipose tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune (e.g. immunodeficiencies, autoimmunities, inflammation, leukemias & lymphomas) and neurological (e.g. Alzheimer's disease, dementia, schizophrenia) disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous, hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., immune, neural, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. The tissue distribution suggests that the protein product of this clone would be useful in the intervention or detection of pathologies associated with the hematopoietic and immune systems, such as anemias (leukemias). In addition, the expression in brain (including fetal) might suggest a role in developmental brain defects, neuro-degenerative diseases or behavioral abnormalities (e.g. schizophrenia, Alzheimer's, dementia, depression, etc.).

30 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 201 as residues: Phe-64 to Gly-77, Pro-83 to Asp-99.

The tissue distribution in hypothalamus suggests the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, 5 Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in 10 feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. This gene product may be involved in the regulation of cytokine production, 15 antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency 20 diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue 25 injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the 30 expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, the protein



product of this clone is useful for the diagnosis, prevention, and/or treatment of various metabolic disorders which include, but are not limited to, Tay-Sachs disease, phenylketonuria, galactosemia, hyperlipidemias, porphyrias, and Hurler's syndrome. The protein is useful in the treatment and/or prevention of neurodegenerative conditions, particularly those which occur secondary to aberrant fatty acid metabolism (i.e. defects which affect the synthesis and integrity of the myelin sheath). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2001 of SEQ ID NO:104, b is an integer of 15 to 2015, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 95**

The translation product of this gene was shown to have homology to the murine leucine-rich repeat protein (See Genbank Accession No. gil2880079), which is thought to be important in neural development.

In specific embodiments, the polypeptides of the invention comprise the sequence: QKPTFALGELYPPLINLWEAGKEKSTSLKVKATVIGLPTNMS (SEQ ID NO:392). Polynucleotides encoding this polypeptide are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

It has been discovered that this gene is expressed primarily in T-cells and brain.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and other hematopoietic disorders, neurological diseases of the brain such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, dementia and specific brain tumors. Similarly, polypeptides and antibodies  
10 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, and cancerous and wounded tissues)  
15 or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
20 202 as residues: Met-24 to Gly-29, Ala-57 to Thr-63.

The tissue distribution in T-cells suggests that the protein product of this clone would be useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders. In addition this  
25 gene product may be applicable in conditions of general microbial infection, inflammation or cancer. The expression in brain, combined with the homology to the leucine-rich repeat protein suggests that the protein product of this clone would be useful for the treatment and diagnosis of developmental, degenerative and behavioral conditions of the brain and nervous system, such as depression, schizophrenia,  
30 Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette Syndrome, mania, dementia, paranoia, addictive behavior, obsessive-compulsive disorder and

sleep disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
5 related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
10 general formula of a-b, where a is any integer between 1 to 353 of SEQ ID NO:105, b is an integer of 15 to 367, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HKGCR51	209628 02/12/98	pSportI	11	2343	1	2343	94	94	108	1	34	35	74
2	HPMDK28	209628 02/12/98	Uni-ZAP XR	12	1177	1	1083	58	58	109	1	27	28	201
3	HLDCD04	209628 02/12/98	pCMVSPORT 3.0	13	2107	197	2107	397	397	110	1	32	33	371
3	HLDCD04	209628 02/12/98	pCMVSPORT 3.0	106	1889	1	1889	193	193	203	1	32	33	57
4	HLDON23	209628 02/12/98	pCMVSPORT 3.0	14	1262	208	1256	368	368	111	1	20	21	113
5	HLDRM43	209628 02/12/98	pCMVSPORT 3.0	15	759	1	759	164	164	112	1	20	21	151
6	HLQAM28	209628 02/12/98	Lambda ZAP II	16	1810	1	1810	43	43	113	1	36	37	55
7	HLTDE74	209628 02/12/98	Uni-ZAP XR	17	1052	1	967	106	106	114	1	20	21	236
8	HLTFA64	209628 02/12/98	Uni-ZAP XR	18	1130	1	1130	268	268	115	1	42	43	43
9	HMC FY13	209628 02/12/98	Uni-ZAP XR	19	883	1	883	175	175	116	1	30	31	64

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
10	HMMBD35	209628 02/12/98	pSport1	20	989	169	989	237	237	117	1	20	21	117
11	HMQCY03	209628 02/12/98	Uni-ZAP XR	21	495	1	495	185	185	118	1	14	15	64
12	HMSBX84	209628 02/12/98	Uni-ZAP XR	22	2317	1	2317	57	57	119	1	20	21	42
13	HMSKI86	209628 02/12/98	Uni-ZAP XR	23	1726	1	1726	84	84	120	1	24	25	47
14	HMVBS81	209628 02/12/98	pSport1	24	529	1	529	34	34	121	1	43	44	139
15	HMWEB02	209628 02/12/98	Uni-Zap XR	25	1755	1	1755	106	106	122	1	23	24	91
16	HMZAD77	209628 02/12/98	pSport1	26	1751	1	1451	49	49	123	1	34	35	346
17	HNF1Y77	209628 02/12/98	pBluescript	27	1212	28	1212	228	228	124	1	34	35	233
18	HNHEK85	209628 02/12/98	Uni-ZAP XR	28	1112	1	1112	35	35	125	1	23	24	53
19	HNHEU93	209628 02/12/98	Uni-ZAP XR	29	748	1	748	57	57	126	1	34	35	81
20	HODAH74	209628 02/12/98	Uni-ZAP XR	30	778	1	778	163	163	127	1	21	22	41

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
21	HODCU34	209628 02/12/98	Uni-ZAP XR	31	1324	1	1324	229	229	128	1	25	26	65
22	HODCZ09	209628 02/12/98	Uni-ZAP XR	32	739	9	739	225	225	129	1	43	44	49
23	HOEDB32	209628 02/12/98	Uni-ZAP XR	33	1462	73	1462	104	104	130	1	21	22	226
24	HOGAG15	209628 02/12/98	pCMVSPORT 2.0	34	2815	1	2815	411	411	131	1	17	18	117
25	HPIBO48	209628 02/12/98	Uni-ZAP XR	35	1078	1	1076	77	77	132	1	31	32	305
26	HPMFP40	209628 02/12/98	Uni-ZAP XR	36	1217	1	1217	37	37	133	1	24	25	44
27	HPRCU95	209628 02/12/98	Uni-ZAP XR	37	1282	1	1282	138	138	134	1	30	31	43
28	HPTTG19	209628 02/12/98	Uni-ZAP XR	38	559	1	559	215	215	135	1	16	17	49
29	HPTVX32	209628 02/12/98	pBluescript	39	803	215	803	318	318	136	1	27	28	80
30	HRDDV47	209628 02/12/98	Uni-ZAP XR	40	1510	1	1510	146	146	137	1	31	32	276
31	HRDEN56	209628 02/12/98	Uni-ZAP XR	41	1095	1	1095	84	84	138	1	26	27	56

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
32	HSFAN12	209641 02/25/98	Uni-ZAP XR	42	1162	1	1162	39	39	139	1	36	37	70
33	HSQCM10	209641 02/25/98	Uni-ZAP XR	43	657	1	654	130	130	140	1	19	20	62
34	HSVAT68	209641 02/25/98	Uni-ZAP XR	44	1155	1	1155	63	63	141	1	25	26	88
35	HSXEC75	209641 02/25/98	Uni-ZAP XR	45	1112	1	1112	295	295	142	1	33	34	45
36	HTDA154	209641 02/25/98	pSport1	46	4023	1	4023	37	37	143	1	37	38	55
37	HTEIT45	209641 02/25/98	Uni-ZAP XR	47	542	14	542	29	29	144	1	35	36	76
38	HTGBE48	209641 02/25/98	Uni-ZAP XR	48	1495	1	1495	169	169	145	1	18	19	42
39	HTLEP53	209641 02/25/98	Uni-ZAP XR	49	818	1	818	73	73	146	1	45	46	101
40	HTTBI76	209641 02/25/98	Uni-ZAP XR	50	1711	1	1711	133	133	147	1	22	23	133
41	HTWKG71	209641 02/25/98	Lambda ZAP II	51	749	1	749	32	32	148	1	19	20	49
42	HTXDN32	209641 02/25/98	Uni-ZAP XR	52	1091	27	804	120	120	149	1	24	25	63

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
43	HTSGX80	209641 02/25/98	pBluescript	53	2254	1	2254	19	19	150	1	20	21	74
44	HTXEY51	209641 02/25/98	Uni-ZAP XR	54	486	55	486	125	125	151	1	32	33	54
45	HTXFH55	209641 02/25/98	Uni-ZAP XR	55	1270	1	1270	61	61	152	1	40	41	57
46	HTXJW17	209641 02/25/98	Uni-ZAP XR	56	2059	1	2059	149	149	153	1	15	16	52
47	HUFCJ30	209641 02/25/98	pSport1	57	868	1	868	123	123	154	1	29	30	50
48	HWAAP70	209641 02/25/98	pCMVSPORT 3.0	58	986	1	986	26	26	155	1	33	34	66
49	HWABW49	209641 02/25/98	pCMVSPORT 3.0	59	695	1	695	170	170	156	1	23	24	48
50	HWBDP28	209641 02/25/98	pCMVSPORT 3.0	60	314	1	314	132	132	157	1	25	26	61
51	HWDAC39	209641 02/25/98	pCMVSPORT 3.0	61	734	1	734	85	85	158	1	20	21	117
52	HWHGQ49	209641 02/25/98	pCMVSPORT 3.0	62	1410	33	1410	306	306	159	1	22	23	150
53	HJPAD75	209641 02/25/98	Uni-ZAP XR	63	1231	1	1231	60	60	160	1	29	30	91



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
54	HLD RP33	209641 02/25/98	pCMV Sport 3.0	64	612	1	612	215	215	161	1	26	27	41
55	HMSJM65	209641 02/25/98	Uni-ZAP XR	65	2270	1	2231	111	111	162	1	27	28	77
56	HNGFE55	209641 02/25/98	Uni-ZAP XR	66	1283	1	1283	132	132	163	1	15	16	54
57	HNKAA41	209641 02/25/98	pSport1	67	1263	1	1123	142	142	164	1	19	20	89
58	HRAAJ19	209641 02/25/98	pCMV Sport 3.0	68	1617	1	1617	48	48	165	1	20	21	44
59	HSAWV96	209641 02/25/98	Uni-ZAP XR	69	1389	1	1389	278	278	166	1	24	25	44
60	HSBBT37	209641 02/25/98	pBluescript SK-	70	1896	1	1896	100	100	167	1	29	30	65
61	HSDZR57	209641 02/25/98	pBluescript	71	308	1	308	27	27	168	1	27	28	61
62	HUSIT18	209641 02/25/98	pSport1	72	1688	1	1688	343	343	169	1	24	25	46
63	HWBCP79	209641 02/25/98	pCMV Sport 3.0	73	1138	1	1138	233	233	170	1	21	22	105
64	HYAAL70	209641 02/25/98	pCMV Sport 3.0	74	777	1	777	88	88	171	1	41	42	44

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
65	HYAAY86	209641 02/25/98	pCMVSPORT 3.0	75	1060	1	1060	118	118	172	1	26	27	46
66	HAPBS03	209651 03/04/98	Uni-ZAP XR	76	1503	45	1479	252	252	173	1	28	29	41
67	HBJLC01	209651 03/04/98	Uni-ZAP XR	77	872	1	872	87	87	174	1	34	35	46
68	HBLKD56	209651 03/04/98	pSport1	78	573	1	573	90	90	175	1	21	22	40
69	HCENK38	209651 03/04/98	Uni-ZAP XR	79	1509	1	1509	10	10	176	1	28	29	52
70	HCHMX01	209651 03/04/98	pSport1	80	1109	1	1109	104	104	177	1	26	27	249
71	HCHNF25	209651 03/04/98	pSport1	81	807	1	807	180	180	178	1	30	31	147
72	HE6GA29	209651 03/04/98	Uni-ZAP XR	82	1043	1	1043	142	142	179	1	15	16	47
73	HE6GE84	209651 03/04/98	Uni-ZAP XR	83	1173	1	1173	334	334	180	1	14	15	55
74	HETHO95	209651 03/04/98	Uni-ZAP XR	84	1561	1	1561	309	309	181	1	24	25	48
75	HFCFJ18	209651 03/04/98	Uni-ZAP XR	85	1433	170	1433	206	206	182	1	25	26	45

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
76	HFPBM30	209651 03/04/98	Uni-ZAP XR	86	1377	1	1377	144	144	183	1	35	36	40
77	HFXKT05	209651 03/04/98	Lambda ZAP II	87	1715	1	1715	204	204	184	1	18	19	79
78	HKB1E57	209651 03/04/98	pCMVSPORT 1	88	417	1	417	30	30	185	1	26	27	46
79	HLWAD77	209651 03/04/98	pCMVSPORT 3.0	89	1167	304	1167	326	326	186	1	24	25	140
80	HLWAY54	209651 03/04/98	pCMVSPORT 3.0	90	1892	1	1892	38	38	187	1	25	26	338
81	HNGBU28	209651 03/04/98	Uni-ZAP XR	91	523	57	523	230	230	188	1	26	27	65
82	HOUHH51	209651 03/04/98	Uni-ZAP XR	92	1382	630	1296	57	57	189	1	35	36	360
82	HOUHH51	209651 03/04/98	Uni-ZAP XR	107	1201	1	815	172	172	204	1	1	2	161
83	HRAAB15	209651 03/04/98	pCMVSPORT 3.0	93	1747	1	1747	35	35	190	1	14	15	159
84	HSAVH65	209651 03/04/98	Uni-ZAP XR	94	600	1	600	104	104	191	1	24	25	100
85	HSDGN55	209651 03/04/98	Uni-ZAP XR	95	586	1	586	177	177	192	1	26	27	42

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
86	HSXAH81	209651 03/04/98	Uni-ZAP XR	96	802	1	802	88	88	193	1	21	22	61
87	HSXBX80	209651 03/04/98	Uni-ZAP XR	97	1226	1	1226	77	77	194	1	22	23	52
88	HTEHV08	209651 03/04/98	Uni-ZAP XR	98	1120	1	1120	382	382	195	1	17	18	185
89	HUFAK67	209651 03/04/98	pSportl	99	2596	1	2596	225	225	196	1	21	22	76
90	HUSXS50	209651 03/04/98	pSportl	100	1020	1	1020	179	179	197	1	23	24	174
91	HAPON17	209651 03/04/98	Uni-ZAP XR	101	1520	1	1520	266	266	198	1	23	24	50
92	HATAC53	209651 03/04/98	Uni-ZAP XR	102	1306	13	1306	99	99	199	1	21	22	189
93	HAMFK58	209641 02/25/98	pCMVSPORT 3.0	103	785	1	785	279	279	200	1	31	32	79
94	HL YCH68	209641 02/25/98	pSportl	104	2015	34	1571	81	81	201	1	19	20	105
95	HCUHK65	209641 02/25/98	ZAP Express	105	367	1	367	80	80	202	1	26	27	79

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further

below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and  
5 diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or  
10 deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or  
15 deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of  
20 plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can  
25 also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be  
30 isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed

sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the  
5 desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides  
10 produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains  
15 secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced  
20 version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

25

### **Signal Sequences**

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal  
30 charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the

information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two  
5 methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a  
10 protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes  
15 vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely  
20 uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the  
25 naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

### 30 Polynucleotide and Polypeptide Variants



"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

5 By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence  
10 at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire  
15 sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known  
20 computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences  
25 are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty  
30 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95%

"identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the the

query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter

the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced  
5 for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an  
10 organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA  
15 technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after  
20 deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological  
25 activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every  
30 possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See,

Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used.

(Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

#### **Polynucleotide and Polypeptide Fragments**

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-



1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or  
5 smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid  
10 sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-  
15 40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

20 Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the  
25 mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

30 Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and

alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.

- 5 Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

### **Epitopes & Antibodies**

- 15 In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).)

- 20 Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

- 25 In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier-protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')<sub>2</sub> fragments) which are capable of specifically binding to protein. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

### **Fusion Proteins**

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous

functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., *Nature* 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See,

D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide.

- 5 In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE-vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein.
- 10 Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

15

#### **Vectors, Host Cells, and Protein Production**

- The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral
- 20 vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

- The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate,
- 25 such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

- The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac
- 30 promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The

expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography,

phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

5 Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant,  
10 insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine  
15 encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

20 In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide  
25 sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24,  
30 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al.,

Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

5

### **Uses of the Polynucleotides**

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

10 The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

15 Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids  
20 containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides  
25 can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved  
30 using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however,



polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

5 For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

10 Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. 20 First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this 25 polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using 30 polynucleotides of the present invention. Any of these alterations (altered expression,

chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods  
5 rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J.  
10 Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can  
15 be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate  
20 manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel.  
25 In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA  
30 markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using  
5 this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification  
10 techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co.  
15 (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

20 There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by  
25 organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences  
30 in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA

antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

### Uses of the Polypeptides

5           Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M.,  
10 et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such  
15 as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo  
20 imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for  
25 the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or  
30 intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety

needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein.

- 5 In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments:" (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which  
10 involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

15 Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to  
20 activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can  
25 also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as  
30 molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also

be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

5

### **Biological Activities**

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules  
10 may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

### **Immune Activity**

A polypeptide or polynucleotide of the present invention may be useful in  
15 treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or  
20 disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in  
25 treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes  
30 include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency,

Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

5           Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood  
10           coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

15           A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the  
20           present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

          Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic  
25           anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary  
30           Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

### 25 Hyperproliferative Disorders

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.



For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune  
5 response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to  
10 neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by  
15 a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia,  
20 located in an organ system listed above.

### **Infectious Disease**

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response,  
25 particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

30 Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the

present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis,

opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See,

Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

### Chemotaxis

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable

of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a

candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

### **Other Activities**

A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%

identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of  
5 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of  
10 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the  
15 range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
20 sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

25 A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X  
30 in Table 1.



A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under  
5 stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which  
10 comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
15 sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of  
20 at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

25 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule  
30 comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X  
5 wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and  
10 determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence  
15 selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

20 A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X  
25 wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological  
30 sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least

one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in

the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence  
5 at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a  
10 polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained  
15 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group  
20 consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least  
25 one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence  
30 selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide

comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit  
5 with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

10 Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is  
15 any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell  
20 type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

25 Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least  
30 one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino

acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

5 In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at  
10 least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number  
15 shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide  
20 comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

25 Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

30 Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is

expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

20

### Examples

#### Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

30



	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited</u>
	<u>Plasmid</u>	
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
5	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
10	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1
	<p>Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.</p>	
	<p>Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain</p>	

XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al.,  
5 Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional  
10 plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample  
15 may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ  
20 ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with <sup>32</sup>P- $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular*  
25 *Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection  
30 agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for

bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the  
5 SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the  
3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired  
cDNA using the deposited cDNA plasmid as a template. The polymerase chain  
reaction is carried out under routine conditions, for instance, in 25 µl of reaction  
mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is  
10 1.5-5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25  
pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR  
(denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1  
min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The  
amplified product is analyzed by agarose gel electrophoresis and the DNA band with  
15 expected molecular weight is excised and purified. The PCR product is verified to be  
the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding  
portions of a gene which may not be present in the deposited clone. These methods  
include but are not limited to, filter probing, clone enrichment using specific probes,  
20 and protocols similar or identical to 5' and 3' "RACE" protocols which are well  
known in the art. For instance, a method similar to 5' RACE is available for  
generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et  
al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a  
25 population of RNA presumably containing full-length gene RNA transcripts. A  
primer set containing a primer specific to the ligated RNA oligonucleotide and a  
primer specific to a known sequence of the gene of interest is used to PCR amplify  
the 5' portion of the desired full-length gene. This amplified product may then be  
sequenced and used to generate the full length gene.

30 This above method starts with total RNA isolated from the desired source,  
although poly-A<sup>+</sup> RNA can be used. The RNA preparation can then be treated with

phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction  
5 leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific  
10 to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

#### **Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

15 A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

#### **Example 3: Tissue Distribution of Polypeptide**

20 Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After  
25 labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H)  
30 or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to

manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

5     **Example 4: Chromosomal Mapping of the Polynucleotides**

          An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is  
10    repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in  
15    the particular somatic cell hybrid.

**Example 5: Bacterial Expression of a Polypeptide**

          A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA  
20    sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc.,  
25    Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

          The pQE-9 vector is digested with BamHI and XbaI and the amplified  
30    fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain

M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>).

Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250

mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further  
5 includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains:  
1) a neomycinphosphotransferase gene as a selection marker, 2) an *E. coli* origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a  
10 Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating  
15 the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

20 The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

#### **Example 6: Purification of a Polypeptide from an Inclusion Body**

The following alternative method can be used to purify a polypeptide  
25 expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit  
30 weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM

Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate  
5 is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the  
10 pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA  
15 by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The  
20 filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

25 Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40  
30 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium



acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### **Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System**

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in

Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in  
5 Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment  
10 then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a  
15 commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified  
20 by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™  
25 baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu$ g of BaculoGold™ virus DNA and 5  $\mu$ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu$ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu$ l Lipofectin plus 90  $\mu$ l Grace's medium are  
30 added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded

in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

- 5           After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell
- 10 culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded
- 15 in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

- To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of
- 20 infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of <sup>35</sup>S-methionine and 5 µCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation.
- 25 The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

30   **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a

chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., *Cell* 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo

contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

#### 15 **Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

30 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These

primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

```
GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGC
CCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAAA
CCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGT
GGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG
ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT
GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA
ACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC
CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCT
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)
```

**Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is



possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody  
5 whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the  
10 antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic  
15 chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in  
20 the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

25

#### **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in  
30 Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>·5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>·7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>·7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

5 On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the  
10 polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

#### 15 **Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The  
20 binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in  
25 many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus  
30 upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2,

Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, *Ann. Rev. Biochem.* 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN- $\alpha$ , IFN- $\gamma$ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

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<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u> <u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	<u>STATS</u>	<u>GAS(elements) or ISRE</u>
<u>IFN family</u>						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g	+	+	+	-	1	GAS (IRF1>Lys6>IFP)
IL-10	+	?	?	-	1,3	
<u>gp130 family</u>						
IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
IL-11(Pleiotrophic)	?	+	?	?	1,3	
OnM(Pleiotrophic)	?	+	+	?	1,3	
LIF(Pleiotrophic)	?	+	+	?	1,3	
CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrophic)	?	+	?	?	1,3	
IL-12(Pleiotrophic)	+	-	+	+	1,3	
<u>g-C family</u>						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
<u>gp140 family</u>						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
<u>Growth hormone family</u>						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
<u>Receptor Tyrosine Kinases</u>						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

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To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

25

### **Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells

30



(ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1% Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

5 After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

10 The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source  
15 of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

20 The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

#### **Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate  
25 myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

30 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell

Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

5        Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at  $37^\circ\text{C}$  for 45 min.

10        Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at  $37^\circ\text{C}$  for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

15        These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

20        Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at  $37^\circ\text{C}$  for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

#### **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

25        When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat pheochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor).

- 5 The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene  
10 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified  
15 product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30  
20 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-  
25 inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine  
30 protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine

growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS  
5 (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing ~~1% horse serum and 0.5% FBS~~ with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$   
10 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold  
15 induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

#### **Example 16: High-Throughput Screening Assay for T-cell Activity**

NF- $\kappa$ B (Nuclear Factor  $\kappa$ B) is a transcription factor activated by a wide  
20 variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- $\kappa$ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- $\kappa$ B appears to shield cells from apoptosis), B and T-cell development,  
25 anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- $\kappa$ B is retained in the cytoplasm with I- $\kappa$ B (Inhibitor  $\kappa$ B). However, upon stimulation, I- $\kappa$ B is phosphorylated and degraded, causing NF- $\kappa$ B to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- $\kappa$ B include IL-2, IL-6, GM-CSF, ICAM-1 and  
30 class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- $\kappa$ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- $\kappa$ B would be useful in treating diseases. For example, inhibitors of NF- $\kappa$ B could be used to treat those diseases related to the acute or chronic activation of NF- $\kappa$ B, such as rheumatoid arthritis.

To construct a vector containing the NF- $\kappa$ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- $\kappa$ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:  
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGAC  
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGACTTTCC  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC  
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA  
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTA  
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA  
GCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2- promoter plasmid (Clontech) with this NF- $\kappa$ B/SV40 fragment using XhoI and

HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- $\kappa$ B/SV40/SEAP cassette is removed from the above NF- $\kappa$ B/SEAP vector using restriction enzymes  
5 SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF- $\kappa$ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF- $\kappa$ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly,  
10 the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### **Example 17: Assay for SEAP Activity**

15 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15  $\mu$ l of 2.5x  
20 dilution buffer into Optiplates containing 35  $\mu$ l of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50  $\mu$ l Assay Buffer and incubate at room  
25 temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50  $\mu$ l Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

30 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

**Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

**Example 18: High-Throughput Screening Assay Identifying Changes in Small****5 Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants



which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

5           The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

10           For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

          A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To  
15       load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37°C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

          For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml  
20       fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed  
25       once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

          For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

          To measure the fluorescence of intracellular calcium, the FLIPR is set for the  
30       following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;

and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular  $\text{Ca}^{++}$  concentration.

5 **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St.

Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar

- 5 Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

- To prepare extracts, A431 cells are seeded onto the nylon membranes of
- 10 Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM
- 15 Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well
- 20 catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

- Test the filtered extracts for levels of tyrosine kinase activity. Although many
- 25 methods of detecting tyrosine kinase activity are known, one method is described here.

- Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include
- 30 PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and

PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

10 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide.

15 Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

20 Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

#### 25 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine

30

phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

**Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim); and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv.

et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

**Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

10 A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

15 For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

25 Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

30 Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard

curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

5

**Example 23: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1  $\mu\text{g/kg/day}$  to 10  $\text{mg/kg/day}$  of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01  $\text{mg/kg/day}$ , and most preferably for humans between about 0.01 and 1  $\text{mg/kg/day}$  for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1  $\mu\text{g/kg/hour}$  to about 50  $\mu\text{g/kg/hour}$ , either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.



The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's

solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical

compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the

5 polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

**Example 24: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or

10 normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to

15 increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

20

**Example 25: Method of Treating Increased Levels of the Polypeptide**

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as

25 cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense

30 polynucleotide is provided in Example 23.

**Example 26: Method of Treatment Using Gene Therapy**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and  
5 separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS,  
10 penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

15 pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified  
20 using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions  
25 appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with  
30 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector.

The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media,  
5 containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no  
10 selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or  
15 after having been grown to confluence on cytodex 3 microcarrier beads.

#### **Example 27: Method of Treatment Using Gene Therapy - In Vivo**

20 Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter  
25 or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord.  
30 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection

into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

#### **Example 28: Transgenic Animals.**

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-



mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones  
5 containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene  
10 in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory  
15 sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is  
20 to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only  
25 that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the  
30 recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA

expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also  
5 be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more  
10 than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for  
15 screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not  
20 limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### 25 **Example 29: Knock-Out Animals.**

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by  
30 reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding

regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and  
5 Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For  
10 example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological  
15 function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

It will be clear that the invention may be practiced otherwise than as  
20 particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other  
25 disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entirety.

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>180</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>February 12, 1998</u>	Accession Number <u>209628</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>183</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
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Date of deposit <u>February 25, 1998</u>	Accession Number <u>209641</u>
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(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>186</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
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Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>March 4, 1998</u>	Accession Number <u>209651</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
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***What Is Claimed Is:***

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group  
5 consisting of:
  - (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a  
10 polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - 15 (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X,  
20 having biological activity;
  - (f) a polynucleotide which is a variant of SEQ ID NO:X;
  - (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
  - (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
  - 25 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.



2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

5 3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

10 4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

15 5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

20 6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

25 7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30 9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

- 5 (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;
- (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- 10 (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- 15 (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- (i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

25

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

- 30 (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

5 17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

10 18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

15

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

20 (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

25 (a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

30

22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- 5 (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

<110> Human Genome Sciences, Inc., et al.

<120> 95 Human Secreted Proteins

<130> PZ027PCT

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<141> 1999, March 18

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<212> DNA

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&lt;210&gt; 16

&lt;211&gt; 1810

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

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 a t t t t t c t c t c t g g a c t g t g c a t a g c a g t a g c t g t t g t t g g g c t g t g t t c g a a a t g a a 180  
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 g t t g a a c t c g c a g c t g g a c c t t t t g g a a a t a a t g a a a a g t t g c c a g t a g t c a t c a g a g t a 420  
 c c a a a a c t g a t c t a t t t t c t c a g t a a t g a g t g t g t g c c t c a t g c c t g t t t c a a t a t t g g g t 480  
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 <212> DNA  
 <213> Homo sapiens

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 c a t a a g a a t a a a a t g g t t c a c a c c a a t a c a a g t a c t t a g t t g t g g a a a g g g a g a g t a g a a 180  
 g a t a a a a a t g g a g a t t t t c c t g t g c t a c a g g c t t a g t c a a g c t t a t g g t c t a t t t a a t g g 240  
 t t a t c a a a g g c a a t t a a a t a g t g t t g a a t g t t c t g c t t t t a c c t a c a t t t c a t t t t t c a t 300  
 g t a c t t a g t t a c a a a t t g a a c c c t c t t c t a t t t t t t c c t g c c c t g t t t c t g t t t c a t t 360  
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 a a g a t a t a a t g g c t t t g g a t t t t g g g g t g a t t t t c t a c t g t c a g t t t a a a a a a a c t t g 840  
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 <223> n equals a,t,g, or c

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 <212> DNA  
 <213> Homo sapiens

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 agacatcgtg aaatgtatta aagtggctct agctagacag agtgggcatg ccagggtcag 180  
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 <212> DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 21

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aaaaaaaaaac	tcgag					495

&lt;210&gt; 22

&lt;211&gt; 2317

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

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&lt;210&gt; 23

&lt;211&gt; 1726

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 23

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&lt;210&gt; 24

&lt;211&gt; 529

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 24

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&lt;210&gt; 25

&lt;211&gt; 1755

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 25

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&lt;210&gt; 26

&lt;211&gt; 1751

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1520)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1557)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1689)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1729)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1735)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1741)

&lt;223&gt; n equals a,t,g, or c

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 <212> DNA  
 <213> Homo sapiens

<400> 27  
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<210> 28  
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 <212> DNA  
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<220>  
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 <222> (1105)  
 <223> n equals a,t,g, or c

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&lt;210&gt; 29

&lt;211&gt; 748

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 29

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cctgtaatcc	cagctacttg	agaggctgag	acaggagaat	ctcttgaacc	cgggaggtgg	660
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&lt;210&gt; 30

&lt;211&gt; 778

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

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&lt;210&gt; 31

&lt;211&gt; 1324

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

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aaaa												1324

&lt;210&gt; 32

&lt;211&gt; 739

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (732)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 32

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tctcatt	ttt	attttg	ctgg	attgttt	ttt	gtttttt	gct	tcagcatt	ct	tgctttt	gct	300
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&lt;210&gt; 33

&lt;211&gt; 1462

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 33

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&lt;210&gt; 34

&lt;211&gt; 2815

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 34

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&lt;210&gt; 35

&lt;211&gt; 1078

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 35

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<210> 36  
<211> 1217  
<212> DNA  
<213> Homo sapiens

<400> 36  
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aaaaaaaaa aaaaaaa 1217

<210> 37  
<211> 1282  
<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (153)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1220)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1222)  
<223> n equals a,t,g, or c

<220>  
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<222> (1232)  
<223> n equals a,t,g, or c

<220>



<221> SITE  
 <222> (1246)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1282)  
 <223> n equals a,t,g, or c

<400> 37

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<210> 38  
 <211> 559  
 <212> DNA  
 <213> Homo sapiens

<400> 38

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<210> 39  
 <211> 803  
 <212> DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 39

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gccagcagaa	ccagccccaa	gccagcacct	ttggtaaata	aagcagcatc	tgagatttta	780
aaaaaaaaaa	aaaaaaactc	gag				803

&lt;210&gt; 40

&lt;211&gt; 1510

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (426)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (454)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 40

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actcttccct	gtgtttgttg	caggagtgtt	tcttttcttt	tatgcaagga	ccctggagtc	240
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aaaaaaaaaa						1510

&lt;210&gt; 41

&lt;211&gt; 1095

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 41

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aaaaaaaaaac	tcgag					1095

&lt;210&gt; 42

&lt;211&gt; 1162

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (340)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 42

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&lt;210&gt; 43

&lt;211&gt; 657

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 43

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caaacatccc	ctggttgggt	atcacttaca	gttgtgtcca	cctttatatt	atgtactttg	600
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&lt;210&gt; 44

&lt;211&gt; 1155

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 44

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aaaaaaaaaa	aaaaa					1155

&lt;210&gt; 45

&lt;211&gt; 1112

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 45

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ctggggcctt	ctcttttccc	agtcaccttt	ggagccacag	aagcagtgtc	ctcattggat	420
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gatttttttt	tacagcgtat	atttctaate	atatttttta	aagccaagag	aactggttga	900
atgaatgttt	attttcctga	aggtattttt	aagataaagc	ttcctaattg	cgtgtaaact	960
ttgcataatg	atgtagtttg	atacatattg	tcacatttga	aaatcttgtg	ggttgtaact	1020
ggttttatac	aaaatctcga	atagtggaaa	ttgtataatt	acaatcatgt	aattaaaagt	1080
attaacccaa	aaaaaaaaaa	aaaaaaytcg	ag			1112

&lt;210&gt; 46

&lt;211&gt; 4023

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1049)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2758)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 46

cccacgcgtc	cgtccaaaca	tcaggaggca	ggcagcatgg	taaatgagaa	agaagccagg	60
actgggagtc	caaagtcctg	gcttctatgt	ctggccttgc	tactaatcaa	atatgtgact	120

ttttgcaaac	catacctcac	taaacccttac	tttcttcatt	tgagcgtgtt	ggaccagctg	180
tccccaggaa	cccccttga	ttgatctgag	aaggcaagga	taagtttttc	aaaggaagaa	240
aagaggagta	gtcagtcgc	agtacagtag	acacaagccc	caggacatct	gagtgtcttt	300
cagcaagaac	tctctgtgat	atttcactac	aatttctctg	gcacctggg	actctcctca	360
gcccttgtgg	tgggtgggtct	tgtttaacta	gcagttccct	ccattctatg	cctgtgaaga	420
atctatcacc	taccatgtga	ttacagtgc	gatttttttt	tccttttctt	tttctttttc	480
tttctttttt	tttttttttt	tgtttgagac	ggagtctcgc	tttgtcacc	aggctgcagc	540
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cccgccctac	agtgcggata	ttttatgaga	gaggagatca	caactcagtc	cccaagccct	840
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ctcaagatga	gaaaactgct	gatgaggctc	actttctaaa	ataccggaat	ttgcaatata	960
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aagcactagt	taaatgtgta	gcgtatttta	agattctgtt	gtatgtacaa	ttgttttagca	2580
gtctctctct	ctttctttct	ctttctttta	tcagagatag	atgattttcc	ctcttatttc	2640
caccagtttg	gcttttcagg	gaagggtggc	gctggcagaa	tcccctgaca	acaaaaggta	2700
cagcaaaaaa	gtggaggcct	aaagaaaaca	tgtgctagct	cttttagcccc	tgaatagnta	2760
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catgccgtgg	caccaagtaa	gcactcaata	aatcactcaa	ctccttttaa	aaaaaaaaa	4020
aaa						4023

&lt;210&gt; 47

&lt;211&gt; 542

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (389)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 47

agggcacgag	tttttttatg	actacataat	gtttattgag	atctatttta	aggcttttca	60
tggatctttt	cagctatgca	catggttagt	cataatgatt	gtcatttttag	gtcagagtgt	120
ctcagcctta	gcattgttga	catttttggt	aattctttgt	tgtaggggct	gtcctgtaca	180
ctgtaggggtg	tttagcagca	tccctgatct	ctacctacta	aatgccagga	gcaacacagt	240
acctccagct	cagttgtgac	aactactgaa	tgtctccaga	caactactga	atgtctccag	300
acattgcaga	gaaattgagt	ctggttgaga	agtcactgtt	ttagggcata	atttttgggt	360
agactgttag	attctttgtg	ttcgttgtnt	ctggcctgta	taactcttct	taattatctg	420
ctactcaa	gtatttggga	tcagccactg	tcttccattt	ctcttttgct	cacagatcta	480
ctccacagct	cttctccctt	caaacactgt	tcctcagcat	cttggtttttt	gcagccaaac	540
at						542

&lt;210&gt; 48

&lt;211&gt; 1495

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 48

cggcacgagg	ctacttatat	tttatgaagg	acattttttg	ttagatgata	tcacccctctg	60
tgttatttgt	tgattgggtt	tgttttttgc	ttgttggttt	gtttgtttct	tccatgtaag	120
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tcaatgttct	tacacattgt	attactgcat	tgtggtaata	gcttctataa	aatctgccat	240
agctgggatt	atgcagcttt	gcaagaatct	actagatttt	attctaactc	atattagctt	300
gtcctatcaa	cttctggaat	tatctaatta	ttgcttttaa	aagtttctctg	cctttcaacg	360
tttccctgct	atgcaaaacc	tttcccagac	cttggtttct	taaaagaaag	atgttgctac	420
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ctaataagc	ccattccctt	ttgtacatga	agatgtcact	taaacctatg	tttacaact	540
aaagagacta	atcactcaat	atgaaaacat	gaaaacattt	ttgcttaaaa	tattaagatg	600
gaaatagtta	aatatggatt	attttgtcct	tttacttttt	aaaaaaagtt	acatattgta	660
tgcactgtgc	tgatgcaaga	attctacatt	ttaatgaatt	ataaaattat	tctgcatctc	720
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ctagaaaaat	aaagtaatgt	ttttgacatt	ggatttggtg	cagtttctaa	tgaagcaatg	960
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gagcttttag	ctttcaaaa	taatttttga	aaaacataca	ttcctggcca	ggtgtggttg	1200
gccacgcctg	taaccccagc	actttgggag	gccgagggag	gggggatcac	ctgaggtcag	1260
gaatttgaga	ccaacctggc	caacatgggt	aaaccccatc	tctactaaaa	gtacaaaaat	1320
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atcacttgaa	cctgggaggt	ggaggttgca	gtgagccgtg	atcacgccat	tgactccag	1440
cctggggggac	aagagtgaga	cttcattctca	aaaaaaaaaa	aaaaaaaaaa	aaaaa	1495

&lt;210&gt; 49

&lt;211&gt; 818

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 49

aaaacttgag	tatgttgagg	gaaggaatat	atatatatct	gggagagaat	ggatacgttt	60
tgtttttctg	aatggaatt	agaaagatgt	tcagttgtct	tgtgcattct	tgcaaacctt	120
gcagttttga	gagccctgtt	tctgccttgt	atcattttcc	actgtgtatc	kgattctagg	180
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ttactgtcaa	gtaaaatata	tttttatgtg	ttttcattgt	gctgaagaaa	aactaatttc	480
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tgggagacca	aggcaggcag	atcacttgag	gtcaggtgtt	cgagaacagc	ctggccaaca	600
tggcaaaacc	ctgtctctac	taaaaatata	aaaattagct	gggtgtggtg	gtacatgcct	660
gtaatcccag	ccacttgagg	ggctgaggca	ctagaattgt	ttgaacctga	gagatggagg	720
ttgcagttag	ctgagattgc	accactgcac	tccagcctgg	gtgacagggg	gacagagcga	780
gactctgtct	caaaaaaaaa	aaaaaaaaaa	aactcgag			818

&lt;210&gt; 50

&lt;211&gt; 1711

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 50

ggcacgagcg	ctcctgtcct	gccactgagg	gacccgggta	ccaaccctca	tgtagctcag	60
tttgcccatc	tgtcccgggtg	ctaacacaca	gttctcggga	gactttcccc	attcccagag	120
gagtagtgcg	aaatgcgtgt	acctctagtc	ttaagctggg	cgtttgattt	agttgggttt	180
tctggtgtct	atttagcaag	tgaaagtttc	tggttccctc	cttcactgtg	tgacctgact	240
agtcctcctg	gattgcattt	atggaagttt	atacgagacc	tagtttccat	ggaggaactc	300
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ccagtgtcct	ctgggtgttt	ccaagagcgg	caagaaacga	ataaatctct	gacccttctc	420
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gtcactaaac	caccaccac	tgccacagct	gcctacaaca	gacacatcag	atgacactcc	540
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gaagtccctc	aacctattgt	gcaacgagtt	ttgagaagcg	ggtaagctgt	atgttttgtg	660
gtttttgttt	ataaattcat	ctacaggaag	accaatattg	actgaatgaa	gcttttcattt	720
aaagagctaa	aatatgcttt	gtgtttttat	atgtggatac	tactttaaac	ctaacgacta	780



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aagtgaatt	catattaaaa	ctgaagattt	tagttacaag	aactgagtg	agattaagtc	1080
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gtattgctct	aaaaaaaaaa	aaaaaaaaaa	a			1711

&lt;210&gt; 51

&lt;211&gt; 749

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 51

gccaaaccag	rtaataat	ctttataata	catgaagtcg	ttatttttgc	tttattttct	60
taggtggcca	atgggggtat	cttgggggga	gacttttata	ctcctaaggg	acagcttggc	120
cattaacttt	caaagtttct	ctaaagcagc	gtcaggagat	atatttggtt	gtcatgacta	180
gtggcattcc	actgacatgt	aatgggtaga	ggctgggtag	acatcctacg	atgcacaaga	240
cagcctccca	caataaagaa	ctgtgtggcc	caaaaatatc	agtgatgctg	agattgagaa	300
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gcaggagagg	tgcttgaacc	cgggagatgg	aggttgcaat	gagccgagat	tatgccattg	660
cactccagcc	tgggtgacag	agtgaagaca	aaaaaaaaaa	aaaaaactcg	agggggggcc	720
cgggtaccaa	ttcgccctat	aggcagtc				749

&lt;210&gt; 52

&lt;211&gt; 1091

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1079)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 52

ggccagtggg	cagggtcaca	gggcaaggtc	ccgcggggccg	ctgggtgcgg	cgacttccgt	60
gctcccggcg	agcgggcgga	gagcgggggc	cgcactgggg	agtgtgggct	gggccgcaga	120
tgtcatgtgg	cctgtktttt	ggaccgtggt	tctacctat	gtcccttatg	tcacattccc	180
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acatctaatt	ggctttgttg	cttattctgg	cccttcccac	accacacagc	cacacaaata	540
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ggccgcacat	gttgtgtggt	ggccacaagc	actcaggcat	ctgagtttac	tgggtgactg	660
ctgggaggag	agttatgaga	tgaacattgg	ctgtcaatct	ctgtgggcag	gcggtttggc	720
ctctagtggg	aatggctggg	atttgggcgt	tgcctttagg	agggatacct	gcagtgtctag	780
ttccagtctg	cactggaaaag	aattcaaata	tgcacctggc	tcccttcact	attttgccct	840
atcctttgtg	ctcattctta	ctgaaatctg	tcttgctcagc	tcaggaatgg	gattccccca	900
ggaaggaaaag	cactttttctg	ttctgggaag	cccagactgt	tcactttggg	gcagggacga	960
acatgtgcct	cgtgaatttg	cttgaaaaca	gtcaccatct	tctacccccca	tcactgtata	1020
gtgaaaaacc	tgattaaagt	ggtatctgag	aaccawaaaa	aaaaaaaaaaa	aaaactcgng	1080
ggggggcccg	g					1091

&lt;210&gt; 53

&lt;211&gt; 2254

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1182)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 53

ggcacgaggc	ccgctgcaat	gttatcatca	cccaacctcg	ccgcacatct	gctgtgtctg	60
tggcacagcg	ggtcagccac	gaactgggcc	cctccctgcg	ccggaatgtg	ggcttccagg	120
tgcggttgga	aagtaagccc	ccatcccagag	gcggggccct	gctcttctgc	actgtgggta	180
tcctgctgcg	taastgcaga	gcaaccccag	cctggaggggc	gtgagccacg	tcctcgtgga	240
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 <212> DNA  
 <213> Homo sapiens

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 <213> Homo sapiens

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gtccttgag	aatctcatta
atcctaggaa	atgggcacta
ggcacagaga	gattaagtac
ttgaacccsg	gagtttttag
gggaggragg	gtgaagcaag
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tggaattcaa	gctttgccac
aatgagatc	atctctgtaa
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<210> 56

<211> 2059

<212> DNA

<213> Homo sapiens

<400> 56

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<211> 868

<212> DNA

<213> Homo sapiens

<400> 57

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&lt;210&gt; 58

&lt;211&gt; 986

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (592)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (669)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (767)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 58

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 <212> DNA  
 <213> Homo sapiens

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 aaaaaaaaaa aagg 314

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 <212> DNA  
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&lt;210&gt; 64

&lt;211&gt; 612

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 64

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&lt;210&gt; 65

&lt;211&gt; 2270

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 65

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&lt;210&gt; 66

&lt;211&gt; 1283

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 66

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&lt;210&gt; 67

&lt;211&gt; 1263

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1256)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 67

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tatgttttct	aaaatgagac	aaatacggat	gtctatttgc	cttttattgt	aacttttaaa	960
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ttg						1263

&lt;210&gt; 68

&lt;211&gt; 1617

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1578)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1586)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1605)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 68

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<210> 69  
 <211> 1389  
 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (755)  
 <223> n equals a,t,g, or c  
  
 <220>  
 <221> SITE  
 <222> (1177)  
 <223> n equals a,t,g, or c

<400> 69						
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<210> 70  
 <211> 1896  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1802)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1856)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1886)  
 <223> n equals a,t,g, or c

<400> 70						
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&lt;210&gt; 71

&lt;211&gt; 308

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 71

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aaaaaaaa						308

&lt;210&gt; 72

&lt;211&gt; 1688

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (912)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 72

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aagaatgctg	ccttgtctgt	ggacaaagat	ggacctgtg	cccttcggaa	ttagggatag	240
aaacaaatat	tgtgtgctct	taacgattaa	gctgtgttat	ggtgggtttt	caggttttta	300
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taaacatc						1688

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<210> 73
<211> 1138
<212> DNA
<213> Homo sapiens
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[illegible]

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<210> 74
<211> 777
<212> DNA
<213> Homo sapiens
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<220>
<221> SITE
<222> (761)
<223> n equals a,t,g, or c
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<400> 74							
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aacttcgwtt	tcttgatgat	tcaggggaaa	agaattctga	gtgttggaag	ggactttaga	720
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<210> 75  
 <211> 1060  
 <212> DNA  
 <213> Homo sapiens

<400> 75						
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aacattttac	atttctaata	taacctcatc	gacctgttaa	aaggcaatat	aagatttaga	240
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attgcaacgt	tatgtctgat	tttttttgkt	gcaaagcttt	cagaatcttg	acttgtggta	360
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tctaggattt	tttttttgcg	taatcatgag	ttacggtggt	aaagttatag	tgtaatttta	600
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<210> 76  
 <211> 1503  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (6)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (18)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (41)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE

&lt;222&gt; (1501)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 76

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tgggctgaag	aaatcactat	tgtgtatata	ctcaagtctt	tttatttttc	ctcttttcat	960
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atgtgattgt	atttccaatt	tcttgttcat	gtaagatttc	aataaaacta	aaaaatctat	1440
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nna						1503

&lt;210&gt; 77

&lt;211&gt; 872

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (844)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (858)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 77

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tggaggccag	agacacttag	gcatattttc	cctccagact	agaagcttct	gaggaggacc	300
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<210> 78  
 <211> 573  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (560)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (563)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (566)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (567)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (571)  
 <223> n equals a,t,g, or c

<400> 78	
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aattattatt	ttggaatgta
agtcattttc	ttcatgaggt
tcatgcattt	tattgcccct
gtgatattga	tgatcctgac
gctgacaaaa	aaaaaaaaan
	aanaannaaa
	naa
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	360
	420
	480
	540
	573

<210> 79  
 <211> 1509

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

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aaaaaaaaaa						1509

&lt;210&gt; 80

&lt;211&gt; 1109

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 80

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<210> 81  
 <211> 807  
 <212> DNA  
 <213> Homo sapiens

<400> 81						
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aggcacgagg	cctgtggagt	aggtccctct	gttccgacag	gtgcgacact	tggcgctcca	180
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<210> 82  
 <211> 1043  
 <212> DNA  
 <213> Homo sapiens

<400> 82						
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<210> 83  
 <211> 1173  
 <212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (548)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (603)

<223> n equals a,t,g, or c

<400> 83

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tttaacctta	tgatggatat	tttgggtgat	ttcagtatta	caaaaatgcc	tattaatagt	300
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<210> 84

<211> 1561

<212> DNA

<213> Homo sapiens

<400> 84

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&lt;210&gt; 85

&lt;211&gt; 1433

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 85

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&lt;210&gt; 86

&lt;211&gt; 1377

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 86

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&lt;210&gt; 87

&lt;211&gt; 1715

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 87

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&lt;210&gt; 88

&lt;211&gt; 417

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 88

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&lt;210&gt; 89

&lt;211&gt; 1167

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (432)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 89

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&lt;210&gt; 90

&lt;211&gt; 1892

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 90

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&lt;210&gt; 91

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 91

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<210> 92  
 <211> 1382  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1382)  
 <223> n equals a,t,g, or c

<400> 92  
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 <223> n equals a,t,g, or c

<220>  
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<220>  
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&lt;213&gt; Homo sapiens

&lt;400&gt; 95

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&lt;210&gt; 96

&lt;211&gt; 802

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 96

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&lt;210&gt; 97

&lt;211&gt; 1226

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 97

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&lt;210&gt; 98

&lt;211&gt; 1120

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

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&lt;210&gt; 99

&lt;211&gt; 2596

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 99

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&lt;210&gt; 100

&lt;211&gt; 1020

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 100

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&lt;210&gt; 101

&lt;211&gt; 1520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (473)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 101

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aacttatttt	ccctggagtc	ttgtgaagtg	tgaatttaaa	gcctgctcta	tctggaatat	1440
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aaaaaaaaat	gaccctcgag					1520

&lt;210&gt; 102

&lt;211&gt; 1306

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1300)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 102

aattccccggg	tcgacccacg	cgtccggaat	ttaagggacc	cacactacct	tcccgaagtt	60
gaaggcaagc	ggtgattggt	tgtagacggc	gctttgtcat	gggacctgtg	cgggttgggaa	120
tattgctttt	cctttttttg	gccgtgcacg	aggcttgggc	tgggatgttg	aaggaggagg	180
acgatgacac	agaacgcttg	cccagcaa	gcgaagtgtg	taagctgctg	agcacagagc	240
tacaggcgga	actgagtcgc	accggtcgat	ctcgagaggt	gctggagctg	gggcaggtgc	300
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gctcactgag	atatgccaa	ggtcagagtc	agaccatggc	aacactgaaa	ggcctagtgc	480
agaagggggg	gaaggtggat	ctggggatcc	ctctggagct	ttgggatgag	cccagcgtgg	540
aggtcacata	cctcaagaag	cagtgtgaga	ccatgttgga	rgargaggag	gaagaggagg	600
aagaggaagg	gggagacaag	atgaccaaga	caggaagcca	ccccaaactt	gaccgagaag	660
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gcctgcactc	tccctgctcc	acagctttca	gggtgtgttt	atgagtgact	ccaccaagc	780
ttgtagctgt	tctctcccat	ctaacctcag	gcaagatcct	ggtgaaacag	catgacatgg	840
cttctggggg	ggaggggtgg	ggtggaggtc	ctgctcctag	agatgaactc	tatccagccc	900
cttaattggc	aggtgtatgt	gctgacagta	ctgaaagctt	tcctctttaa	ctgatcccac	960
ccccacccaa	aagtcagcag	tggcactgga	gctgtgggct	ttggggaagt	cacttagctc	1020
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tatatacatt	gcctgtatcc	aggaggctac	acaccagcaa	accgtgaagg	agaatgggac	1140
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gctcaatgta	acccagagcc	caccatatag	ttttataggt	gctcaatttt	ctatatcgct	1260
attaaacttt	tttctttttt	tctaaaaaaa	aaaaaaaaan	actcga		1306

&lt;210&gt; 103

&lt;211&gt; 785

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 103

cttttagaag	gtacgcctgc	aggtaccggt	ccggaattcc	cgggtcgacc	cacgcgtccg	60
ggaaatgaac	taccatttat	aacttctgtt	tttttattga	gaaaatgatt	cacgaattcc	120
aaatcagatt	gccaggaaga	aataggacgt	gacggtactg	ggccctgtga	ttctccagc	180
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gggttatggg	agaaaccaga	gatgggaatg	aggaaaatat	gaactacagc	agaagcccct	300
gggcagctgt	gatggagccc	ctgacattac	tcttcttgca	tctgtcctgc	cttctttccc	360
tctgcgaggc	agtgggggtg	gattcagagt	gcttagtctg	ctcactggga	gaagaagagt	420
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tctgtacgtt	ggggactgct	tgtatttgga	agattttaaa	acctagcacc	ctgttctcac	540
cctctaagct	gcattgagaa	atgactcgtc	tctgtatttg	tattaagcct	taacactttt	600
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acatcacaat	gtcatttttg	taggagcggt	ttgttatttt	tacaaggcag	aatgggggtg	720
aacagttgaa	ttaaacttag	caatcacgtg	ctcaaaaaaa	aaaaaaaaaa	aaaaagggcg	780
gccgc						785

&lt;210&gt; 104

&lt;211&gt; 2015

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1981)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1990)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2001)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2002)

<223> n equals a,t,g, or c

<400> 104

ccnggaatnc	cggtcgacc	cacgcgtccg	gcctgcgctg	ccagcagcca	ggagccagga	60
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tggatgtagg	aggagctcaa	gtgctggcaa	caggcaagac	ccctggggct	gaaattgatt	180
tcaagtacgc	cctcatcggg	actgctgtgg	gtgtcgccat	atctgctggc	ttcctggccc	240
tgaagatctg	catgatcagg	aggcacttat	ttgacgacga	ctcttccgac	ctgaaaagca	300
crcttggggg	cctcagtgc	accatcccgc	taaagaagag	agccccaagg	cgaaaccaca	360
atttctccaa	aagagatgca	caggtgattg	agctgtaggt	gagcagtgc	gtgaagaggg	420
gttctagccc	cgtggaaaac	agcccatggt	taacatctca	ggatgtcctg	cattcaaaca	480
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ttcacccctgt	gttggagctg	ttcatgcttc	catgaggcca	tgggtgtccat	gtccgtggaa	720
cctaccacag	aaaatggctc	atgaaaaggg	gaatccgacc	caacacacag	cttctctacac	780
actgccatct	tatcaacagt	taggcactac	tttgtagaac	gattagcttc	accctcttag	840
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gacattctac	aattgccatc	aggctaaggc	cccgtgagca	tttctctccc	ttgtaatat	1260
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gatgtgttc	attagcagcc	tttgtttaact	gataaccaag	agcggtaatg	tgatactcat	1500
aagcaatttt	ctgtgtgtag	gataaaaataa	accatcttgt	atgggaaaaa	aaaaaaaaaa	1560
aaaaaaaaaa	aaaaagggcg	gccgctctag	aggatccaag	cttacgtacg	cgtgcatgcy	1620
acgtcatagc	tcttctatag	tgkacaccta	attcaattca	ctggccgctg	ttttacaacg	1680
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cccttccttt	ctcgccacgt	tcgccgggtt	tccccgtcaa	gctttaaatc	gggggcttcc	1980
nttaagggtg	ccaattaagg	nnttaccggg	acctt			2015

&lt;210&gt; 105

&lt;211&gt; 367

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 105

cggcacgagt	gtaaatgtca	ccaccaaaagg	tttgcaccct	gatcaaaaag	agtatgaaaa	60
gaataatacc	acaacactta	tggcctgtct	tggaggcctt	ctgggggatta	ttggtgtgat	120
atgtcttata	agctgcctct	ctccagaaat	gaactgtgat	ggtggacaca	gctatgtgag	180
gaattactta	cagaaaccaa	cctttgcatt	aggtgagctt	tatcctcctc	tgataaatct	240
ctgggaagca	ggaaaagaaa	aaagtacatc	actgaaagta	aaagcaactg	ttatagggtt	300
accaacaaat	atgtcctaaa	aaccaccaag	gaaacctact	ccaaaaatga	aaaaaaaaaa	360
aaaaaaa						367

&lt;210&gt; 106

&lt;211&gt; 1889

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 106

ctcatccttc	tatcatcata	tggagtggca	ataatgaaaa	tgaggaggcg	ctgatgatga	60
attggtatca	tatcagtttc	actgaccggc	caatctacat	caaggactat	gtgacactct	120
atgtgaaaaa	catcagagag	ctcgtactgg	caggagacaa	gagtcgtcct	tttattacgt	180
ccagtcctac	aaatggggct	gaaactgttg	cagaagcctg	ggtctctcaa	aaccctaata	240
gcaattattt	tggatgatga	cattttttatg	actatatcag	tgattgctgg	aactggaaag	300
ttttcccaaa	agctcgattt	gcattctgaat	atggatatca	gtcctggccg	tccttcagta	360
cattagaaaa	ggtctcgtct	acagaggact	ggtctttcaa	tagcaagttt	tcacttcac	420
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tgcaggccca	gtgtgtcaaa	acagaaactg	aattctaccg	ccgtagtcgc	agcgagatag	600
tggatcagca	agggcacacg	atgggggcac	tttattggca	gttgatgac	atctggcaag	660
ctccttcctg	ggcttctctt	gatacggagg	aaagtggaaa	atgcttcatt	actttgctca	720
gaattttctt	gtccactgt	tgccagtagc	tttgaaatga	aaacatgttc	tatatctatg	780
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ctgtctgcct	ttatgaggag	ccagtgtctg	aattgctgag	gagatgtggg	aattgcacac	960
gggaaagctg	tgtggtttcc	ttttaccttt	cagctgacca	tgaactcctg	agcccgacca	1020
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gtatatggat	atttttctgt	acatgtgaaa	ttatataaaa	ataaaagtta	tataaattac	1860
attgaaaaaa	aaaaaaaaaa	aaaaaaaaaa				1889

&lt;210&gt; 107

&lt;211&gt; 1201

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1086)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1161)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1176)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 107

cggcacgagc	ggctggcagc	acgactcgcg	taccgtgcgc	cgattgcctc	tcggcctggg	60
caatgggtccc	ggctgccggg	cgacgaccgc	cccgcgtcat	gcggctcctc	ggctgggtggc	120
aagtattgct	gtgggtgctg	ggacttcccg	tccgcggcgt	ggagggacct	tatggatttt	180
ctgaacccaa	acggtagtga	ctgtactcta	gtcctgtttt	acaccccgctg	gtgccgcttt	240
tctgccagtt	tggcccttca	ctttaactct	ctgccccggg	catttccagc	tcttcaacttt	300
ttggcactgg	atgcacatca	gcacagcagc	ctttctacca	ggtttggcac	cgtagctggt	360
cctaataattt	tattatttca	aggagctaaa	ccaatggcca	gatttaataca	tacagatcga	420
acactggaaa	cactgaaaat	cttcattttt	aatcagacag	gtatagaagc	caagaagaat	480
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gagtagaatg	acagcttact	atacagaagg	cmaaaatagg	actctcaggt	aatagtttaa	1020
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gtttttnctt	taggagtcga	tagccaggga	aagtatgtga	accagaattg	gttagtgtga	1140
ccccctccaa	gtagccagtg	ntgggaaata	agggtncaat	accttgatgt	ttgtgatctc	1200

t

1201

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<210> 108
<211> 75
<212> PRT
<213> Homo sapiens
```

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<220>  
<221> SITE  
<222> (75)  
<223> Xaa equals stop translation
```

```

<400> 108
Met Asp Pro Leu Cys Leu Pro Ile Ile Leu Phe Ser Ala Val Val Leu
  1             5             10             15
Arg Asn Leu Phe His Leu Leu Ile Leu Thr Phe His Tyr Leu Pro Leu
          20             25             30
Phe Cys Asp Asn Pro Leu Ile Leu Glu Asp Leu Ser Cys Ile His Leu
          35             40             45
Arg Val Asn Ile Phe Lys Ala Lys Gln Pro Lys Phe Tyr Gly Asn Gln
  50             55             60
Leu Gln Pro Cys Val Met Lys Ser Ser Ala Xaa
  65             70             75

```

```
<210> 109
<211> 202
<212> PRT
<213> Homo sapiens
```

```
<220>  
<221> SITE  
<222> (202)  
<223> Xaa equals stop translation
```

<400> 109																
Met	Lys	Leu	Leu	Ile	Leu	Phe	Leu	Ser	His	Leu	Leu	Ser	Leu	Ala	Phe	
1				5					10					15		
Gly	Ile	Leu	Cys	Leu	Ser	Val	Thr	Val	Ile	Leu	Ser	Leu	Leu	Leu	Ser	
			20					25					30			
Phe	Ser	Lys	Arg	Gly	Phe	Ser	Val	Arg	Ser	Phe	Gly	Thr	Gly	Thr	His	
		35					40					45				
Val	Lys	Leu	Pro	Gly	Pro	Ala	Pro	Asp	Lys	Pro	Asn	Val	Tyr	Asp	Phe	
	50					55					60					
Lys	Thr	Thr	Tyr	Asp	Gln	Met	Tyr	Asn	Asp	Leu	Leu	Arg	Lys	Asp	Lys	
65					70					75					80	

Glu Leu Tyr Thr Gln Asn Gly Ile Leu His Met Leu Asp Arg Asn Lys  
                     85                    90                    95  
 Arg Ile Lys Pro Arg Pro Glu Arg Phe Gln Asn Cys Lys Asp Leu Phe  
                     100                    105                    110  
 Asp Leu Ile Leu Thr Cys Glu Glu Arg Val Tyr Asp Gln Val Val Glu  
                     115                    120                    125  
 Asp Leu Asn Ser Arg Glu Gln Glu Thr Cys Gln Pro Val His Val Val  
                     130                    135                    140  
 Asn Val Asp Ile Gln Asp Asn His Glu Glu Ala Thr Leu Gly Ala Phe  
                     145                    150                    155                    160  
 Leu Ile Cys Glu Leu Cys Gln Cys Ile Gln His Thr Glu Asp Met Glu  
                     165                    170                    175  
 Asn Glu Ile Asp Glu Leu Leu Gln Glu Phe Glu Glu Lys Ser Gly Arg  
                     180                    185                    190  
 Thr Phe Leu His Thr Val Cys Phe Tyr Xaa  
                     195                    200

&lt;210&gt; 110

&lt;211&gt; 371

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (193)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 110

Met Gly Leu Lys Leu Leu Gln Lys Pro Gly Ser Leu Lys Thr Leu Ile  
           1                    5                    10                    15

Ala Ile Ile Leu Val Met Tyr Ile Phe Met Thr Ile Ser Val Xaa Cys  
                     20                    25                    30

Trp Asn Trp Lys Val Phe Pro Lys Ala Arg Phe Ala Ser Glu Tyr Gly  
                     35                    40                    45

Tyr Gln Ser Trp Pro Ser Phe Ser Thr Leu Glu Lys Val Ser Ser Thr  
                     50                    55                    60

Glu Asp Trp Ser Phe Asn Ser Lys Phe Ser Leu His Arg Gln His His

65

65		70		75		80
Glu Gly Gly Asn Lys Gln Met Leu Tyr Gln Ala Gly Leu His Phe Lys	85	90			95	
Leu Pro Gln Ser Thr Asp Pro Leu Arg Thr Phe Lys Asp Thr Ile Tyr	100	105			110	
Leu Thr Gln Val Met Gln Ala Gln Cys Val Lys Thr Glu Thr Glu Phe	115	120			125	
Tyr Arg Arg Ser Arg Ser Glu Ile Val Asp Gln Gln Gly His Thr Met	130	135			140	
Gly Ala Leu Tyr Trp Gln Leu Asn Asp Ile Trp Gln Ala Pro Ser Trp	145	150			155	160
Ala Ser Leu Glu Tyr Gly Gly Lys Trp Lys Met Leu His Tyr Phe Ala	165	170			175	
Gln Asn Phe Phe Ala Pro Leu Leu Pro Val Gly Phe Glu Asn Glu Asn	180	185			190	
Xaa Phe Tyr Ile Tyr Gly Val Ser Asp Leu His Ser Asp Tyr Ser Met	195	200			205	
Thr Leu Ser Val Arg Val His Thr Trp Ser Ser Leu Glu Pro Val Cys	210	215			220	
Ser Arg Val Thr Glu Arg Phe Val Met Lys Gly Gly Glu Ala Val Cys	225	230			235	240
Leu Tyr Glu Glu Pro Val Ser Glu Leu Leu Arg Arg Cys Gly Asn Cys	245	250			255	
Thr Arg Glu Ser Cys Val Val Ser Phe Tyr Leu Ser Ala Asp His Glu	260	265			270	
Leu Leu Ser Pro Thr Asn Tyr His Phe Leu Ser Ser Pro Lys Glu Ala	275	280			285	
Val Gly Leu Cys Lys Ala Gln Ile Thr Ala Ile Ile Ser Gln Gln Gly	290	295			300	
Asp Ile Phe Val Phe Asp Leu Glu Thr Ser Ala Val Ala Pro Phe Val	305	310			315	320
Trp Leu Asp Val Gly Ser Ile Pro Gly Arg Phe Ser Asp Asn Gly Phe	325	330			335	
Leu Met Thr Glu Lys Thr Arg Thr Ile Leu Phe Tyr Pro Trp Glu Pro	340	345			350	
Thr Ser Lys Asn Glu Leu Glu Gln Ser Phe His Val Thr Ser Leu Thr	355	360			365	

Asp Ile Tyr  
370

<210> 111  
<211> 114  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (38)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (114)  
<223> Xaa equals stop translation

<400> 111  
Met Arg Pro Leu Leu Leu Gly Gly Tyr Trp Val Leu Cys Leu Ser Val  
1 5 10 15

Leu Gly His Ala Ala Leu Tyr His Phe Trp Leu Arg Glu Glu Gly Lys  
20 25 30

Gly Pro Pro Gln Val Xaa Ser Val Leu Ala Leu Ala Leu Pro Ala Gly  
35 40 45

Ser Cys Ala Pro Gly Leu Pro Phe Pro Gly Pro Leu Ile Pro Thr Gln  
50 55 60

Leu Leu Phe Ala Leu Glu Trp Gly Thr Pro Thr Pro Leu Arg Asp His  
65 70 75 80

Pro Pro His Ser Met His Ser Ala Pro Gln Asn Pro Pro Val Phe Leu  
85 90 95

Gly Thr His Thr Cys Pro Pro Ser Trp Tyr Phe Arg Leu Ile Pro Gln  
100 105 110

Ala Xaa

<210> 112  
<211> 152  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (152)  
<223> Xaa equals stop translation

&lt;400&gt; 112

Met Arg Arg Leu Leu Leu Val Thr Ser Leu Val Val Val Leu Leu Trp  
 1 5 10 15

Glu Ala Gly Ala Val Pro Ala Pro Lys Val Pro Ile Lys Met Gln Val  
 20 25 30

Lys His Trp Pro Ser Glu Gln Asp Pro Glu Lys Ala Trp Gly Ala Arg  
 35 40 45

Val Val Glu Pro Pro Glu Lys Asp Asp Gln Leu Val Val Leu Phe Pro  
 50 55 60

Val Gln Lys Pro Lys Leu Leu Thr Thr Glu Glu Lys Pro Arg Gly Gln  
 65 70 75 80

Gly Arg Gly Pro Ile Leu Pro Gly Thr Lys Ala Trp Met Glu Thr Glu  
 85 90 95

Asp Thr Leu Gly Arg Val Leu Ser Pro Glu Pro Asp His Asp Ser Leu  
 100 105 110

Tyr His Pro Pro Pro Glu Glu Asp Gln Gly Glu Glu Arg Pro Arg Leu  
 115 120 125

Trp Val Met Pro Asn His Gln Val Leu Leu Gly Pro Glu Glu Asp Gln  
 130 135 140

Asp His Ile Tyr His Pro Gln Xaa  
 145 150

&lt;210&gt; 113

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 113

Met Pro Cys Gly Lys Phe Leu Phe Pro Val Ser Pro Val Ser Ser Leu  
 1 5 10 15

Ser Leu His Trp Ser Ala Val Leu Leu Leu Leu Ala Asp Phe Pro  
 20 25 30

Arg Val His Gly Ser Pro Pro Gly Val Ser Arg Val Ser Ile Leu His  
 35 40 45

Cys Leu Phe Pro Phe Leu Ser Xaa  
 50 55

<210> 114  
 <211> 237  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (237)  
 <223> Xaa equals stop translation

<400> 114  
 Met Glu Val Arg Leu Ile Phe Leu Ser Gly Leu Cys Ile Ala Val Ala  
     1                    5                    10                    15  
 Val Val Trp Ala Val Phe Arg Asn Glu Asp Arg Trp Ala Trp Ile Leu  
                     20                    25                    30  
 Gln Asp Ile Leu Gly Ile Ala Phe Cys Leu Asn Leu Ile Lys Thr Leu  
                     35                    40                    45  
 Lys Leu Pro Asn Phe Lys Ser Cys Val Ile Leu Leu Gly Leu Leu Leu  
                     50                    55                    60  
 Leu Tyr Asp Val Phe Phe Val Phe Ile Thr Pro Phe Ile Thr Lys Asn  
                     65                    70                    75                    80  
 Gly Glu Ser Ile Met Val Glu Leu Ala Ala Gly Pro Phe Gly Asn Asn  
                     85                    90                    95  
 Glu Lys Leu Pro Val Val Ile Arg Val Pro Lys Leu Ile Tyr Phe Ser  
                     100                    105                    110  
 Val Met Ser Val Cys Leu Met Pro Val Ser Ile Leu Gly Phe Gly Asp  
                     115                    120                    125  
 Ile Ile Val Pro Gly Leu Leu Ile Ala Tyr Cys Arg Arg Phe Asp Val  
                     130                    135                    140  
 Gln Thr Gly Ser Ser Tyr Ile Tyr Tyr Val Ser Ser Thr Val Ala Tyr  
                     145                    150                    155                    160  
 Ala Ile Gly Met Ile Leu Thr Phe Val Val Leu Val Leu Met Lys Lys  
                     165                    170                    175  
 Gly Gln Pro Ala Leu Leu Tyr Leu Val Pro Cys Thr Leu Ile Thr Ala  
                     180                    185                    190  
 Ser Val Val Ala Trp Arg Arg Lys Glu Met Lys Lys Phe Trp Lys Gly  
                     195                    200                    205  
 Asn Ser Tyr Gln Met Met Asp His Leu Asp Cys Ala Thr Asn Glu Glu  
                     210                    215                    220



Asn Pro Val Ile Ser Gly Glu Gln Ile Val Gln Gln Xaa  
225                      230                      235

<210> 115  
<211> 44  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 115  
Met Phe Cys Phe Tyr Leu His Phe Ile Phe His Val Leu Ser Tyr Lys  
1                      5                      10                      15  
Leu Asn Pro Leu Leu Phe Phe Ser Cys Ser Cys Phe Cys Phe Ile Leu  
                    20                      25                      30  
Val Phe Leu Phe Pro Asp Tyr His Leu Gly Met Xaa  
                    35                      40

<210> 116  
<211> 65  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (65)  
<223> Xaa equals stop translation

<400> 116  
Met Val Arg His Ile Arg Glu Arg Arg Arg Gln Pro Leu Ala Phe Gln  
1                      5                      10                      15  
Arg Val Leu Leu Ser Leu Cys Leu Leu Glu Gly Ile Trp His Ser Pro  
                    20                      25                      30  
Ala Ala Ala Ala Gly Gly Gly Ser His Cys Ser Ser Trp Pro Ser Leu  
                    35                      40                      45  
Tyr Thr Thr Phe Gln Arg Val Ser Leu Leu Glu Leu Asp Leu Gly Leu  
                    50                      55                      60  
Xaa  
65

<210> 117  
<211> 118  
<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (118)

<223> Xaa equals stop translation

<400> 117

Met Ala Arg Ser Ala Leu Arg Leu Glu Ile Leu Gly Gln Leu Leu Val  
1 5 10 15

Gly Val Ser Ser Cys Cys Ala Glu Ile Arg Ser Arg Ser Tyr Leu Gly  
20 25 30

Phe Cys Trp Lys Asn Ile Gln Asp Glu Arg Lys Lys Lys Ile Ile Leu  
35 40 45

Arg Gly Ser Arg Asn Leu Leu Cys Pro Arg Leu Leu Arg Pro Leu Glu  
50 55 60

Pro Val Gln Ala Lys Gly Thr Gln Ser Val Asp Pro Arg Glu Val Val  
65 70 75 80

Arg Glu Thr Arg Ser Met Ser Thr Leu Pro Ala Asp Phe Cys Leu Leu  
85 90 95

Pro Gln Ala Ser Arg Met Ala Gln Lys Gly Ser Pro Ser Arg Ser Ser  
100 105 110

Leu Gln Leu Leu Phe Xaa  
115

<210> 118

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (65)

<223> Xaa equals stop translation

<400> 118

Met Thr Val Ser Leu Phe Leu Leu Leu Ala Thr Ser Gln Ser Gln Asp  
1 5 10 15

Gly Cys Cys Asp Ser Gly Ser Cys Pro Asn Ser Arg Gln Gln Glu Gly  
20 25 30

His Gly Ala Ala Pro Ala Ser Arg Cys Pro Cys Arg Pro Ser Leu Gln  
35 40 45

Ala Gln Glu Pro Lys Glu Glu Ser Thr Gln Met Trp Cys Ser His Leu  
50 55 60

Xaa  
65

<210> 119  
<211> 43  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (43)  
<223> Xaa equals stop translation

<400> 119  
Met Leu Lys Trp Thr Gly Phe Leu Val Val Leu Val Ala Phe Lys Lys  
1 5 10 15  
Ile Ser Ala Ser Phe Gln Val Asn Tyr Asn Leu Lys Phe Glu Ile Ser  
20 25 30  
Phe Gly Glu Pro Trp Lys Phe Thr Gln Trp Xaa  
35 40

<210> 120  
<211> 48  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (48)  
<223> Xaa equals stop translation

<400> 120  
Met Ser Phe Gly Ile Ser Ile His Thr Cys Thr Tyr Leu Ile Phe Ile  
1 5 10 15  
Ala Phe His Phe Ile Ala Leu Cys Lys Val Thr Phe Phe Thr Asp Ser  
20 25 30  
Arg Phe Gly Asn Pro Met Ser Ile Ser Leu Ser Ala Pro Phe Phe Xaa  
35 40 45

<210> 121  
<211> 140  
<212> PRT  
<213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (140)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 121

Met	Ala	Leu	Gly	Ile	Gln	Lys	Arg	Phe	Ser	Pro	Glu	Val	Leu	Gly	Leu
1				5					10					15	

Cys	Ala	Ser	Thr	Ala	Leu	Val	Trp	Val	Val	Met	Glu	Val	Leu	Ala	Leu
			20					25					30		

Leu	Leu	Gly	Leu	Tyr	Leu	Ala	Thr	Val	Arg	Ser	Asp	Leu	Ser	Thr	Phe
		35						40					45		

His	Leu	Leu	Ala	Tyr	Ser	Gly	Tyr	Lys	Tyr	Val	Gly	Met	Ile	Leu	Ser
	50					55					60				

Val	Leu	Thr	Gly	Leu	Leu	Phe	Gly	Ser	Asp	Gly	Tyr	Tyr	Val	Ala	Leu
65					70					75					80

Ala	Trp	Thr	Ser	Ser	Ala	Leu	Met	Tyr	Phe	Ile	Val	Arg	Ser	Leu	Arg
				85					90					95	

Thr	Ala	Ala	Leu	Gly	Pro	Asp	Ser	Met	Gly	Gly	Pro	Val	Pro	Arg	Gln
			100					105					110		

Arg	Leu	Gln	Leu	Tyr	Leu	Thr	Leu	Gly	Ala	Ala	Ala	Phe	Gln	Pro	Leu
		115					120					125			

Ile	Ile	Tyr	Trp	Leu	Thr	Phe	His	Leu	Val	Arg	Xaa
	130					135					140

&lt;210&gt; 122

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (89)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (92)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 122

Met	Met	Asp	Phe	Leu	Arg	Cys	Val	Thr	Ala	Ala	Leu	Ile	Tyr	Phe	Ala
1				5					10					15	

Ile	Ser	Ile	Thr	Ala	Ile	Ala	Lys	Tyr	Ser	Asp	Gly	Ala	Ser	Lys	Ala
			20					25					30		

Ser Pro Val Met His Pro Ile His Pro Val His Arg Cys Leu Ala Ser  
65 70 75 80

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<210> 123
<211> 347
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (242)
<223> Xaa equals any of the naturally occurring L-amino acids
```

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<220>
<221> SITE
<222> (246)
<223> Xaa equals any of the naturally occurring L-amino acids
```

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<220>  
<221> SITE  
<222> (347)  
<223> Xaa equals stop translation
```

<400> 123  
Met Arg Arg Gly Ala Gly Ala Ala Arg Gly Arg Ala Ser Trp Cys Trp  
1 5 10 15

Ala Leu Ala Leu Leu Trp Leu Ala Val Val Pro Gly Trp Ser Arg Val  
20 25 30

Ser Gly Ile Pro Ser Arg Arg His Trp Pro Val Pro Tyr Lys Arg Phe  
35 40 45

Asp Phe Arg Pro Lys Pro Asp Pro Tyr Cys Gln Ala Lys Tyr Thr Phe  
50 55 60

Cys Pro Thr Gly Ser Pro Ile Pro Val Met Glu Gly Asp Asp Asp Ile  
65 70 75 80

Glu Val Phe Arg Leu Gln Ala Pro Val Trp Glu Phe Lys Tyr Gly Asp  
85 90 95

Leu Leu Gly His Leu Lys Ile Met His Asp Ala Ile Gly Phe Arg Ser  
100 105 110

Thr Leu Thr Gly Lys Asn Tyr Thr Met Glu Trp Tyr Glu Leu Phe Gln  
 115 120 125  
 Leu Gly Asn Cys Thr Phe Pro His Leu Arg Pro Glu Met Asp Ala Pro  
 130 135 140  
 Phe Trp Cys Asn Gln Gly Ala Ala Cys Phe Phe Glu Gly Ile Asp Asp  
 145 150 155 160  
 Val His Trp Lys Glu Asn Gly Thr Leu Val Gln Val Ala Thr Ile Ser  
 165 170 175  
 Gly Asn Met Phe Asn Gln Met Ala Lys Trp Val Lys Gln Asp Asn Glu  
 180 185 190  
 Thr Gly Ile Tyr Tyr Glu Thr Trp Asn Val Lys Ala Ser Pro Glu Lys  
 195 200 205  
 Gly Ala Glu Thr Trp Phe Asp Ser Tyr Asp Cys Ser Lys Phe Val Leu  
 210 215 220  
 Arg Thr Phe Asn Lys Leu Ala Glu Phe Gly Ala Glu Phe Lys Asn Ile  
 225 230 235 240  
 Glu Xaa Asn Tyr Thr Xaa Ile Phe Leu Tyr Ser Gly Glu Pro Thr Tyr  
 245 250 255  
 Leu Gly Asn Glu Thr Ser Val Phe Gly Pro Thr Gly Asn Lys Thr Leu  
 260 265 270  
 Gly Leu Ala Ile Lys Arg Phe Tyr Tyr Pro Phe Lys Pro His Leu Pro  
 275 280 285  
 Thr Lys Glu Phe Leu Leu Ser Leu Leu Gln Ile Phe Asp Ala Val Ile  
 290 295 300  
 Val His Lys Gln Phe Tyr Leu Phe Tyr Asn Phe Glu Tyr Trp Phe Leu  
 305 310 315 320  
 Pro Met Lys Phe Pro Phe Ile Lys Ile Thr Tyr Glu Glu Ile Pro Leu  
 325 330 335  
 Pro Ile Arg Asn Lys Thr Leu Ser Gly Leu Xaa  
 340 345

&lt;210&gt; 124

&lt;211&gt; 234

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (173)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (234)

<223> Xaa equals stop translation

<400> 124

Met His Arg Gly Lys Leu Asp Cys Ala Gly Gly Ala Leu Leu Ser Ser  
1 5 10 15

Tyr Leu Ile Val Leu Met Ile Leu Leu Ala Val Val Ile Cys Thr Val  
20 25 30

Ser Ala Ile Met Cys Val Ser Met Arg Gly Thr Ile Cys Asn Pro Gly  
35 40 45

Pro Arg Lys Ser Met Ser Lys Leu Leu Tyr Ile Arg Leu Ala Leu Phe  
50 55 60

Phe Pro Glu Met Val Trp Ala Ser Leu Gly Ala Ala Trp Val Ala Asp  
65 70 75 80

Gly Val Gln Cys Asp Arg Thr Val Val Asn Gly Ile Ile Ala Thr Val  
85 90 95

Val Val Ser Trp Ile Ile Ile Ala Ala Thr Val Val Ser Ile Ile Ile  
100 105 110

Val Phe Asp Pro Leu Gly Gly Lys Met Ala Pro Tyr Ser Ser Ala Gly  
115 120 125

Pro Ser His Leu Asp Ser His Asp Ser Ser Gln Leu Leu Asn Gly Leu  
130 135 140

Lys Thr Ala Ala Thr Ser Val Trp Glu Thr Arg Ile Lys Leu Leu Cys  
145 150 155 160

Cys Cys Ile Gly Lys Asp Asp His Thr Arg Val Ala Xaa Ser Ser Thr  
165 170 175

Ala Glu Leu Phe Ser Thr Tyr Phe Ser Asp Thr Asp Leu Val Pro Ser  
180 185 190

Asp Ile Ala Ala Gly Leu Ala Leu Leu His Gln Gln Gln Asp Asn Ile  
195 200 205

Arg Asn Asn Gln Asp Leu Pro Arg Trp Ser Ala Met Pro Gln Gly Ala  
210 215 220

Pro Arg Lys Leu Ile Trp Met Gln Asn Xaa  
225 230

<210> 125

<211> 54  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (54)  
 <223> Xaa equals stop translation

<400> 125  
 Met Gln Gly Val Leu Phe Gly Phe Val Trp Leu Phe Ser Phe Leu Trp  
           1                  5                  10                  15  
 Gln Glu Asn Lys Ser Ser Ala Ser Pro Ser Thr Leu Ala Lys Ser Gly  
                   20                  25                  30  
 Ser Pro Cys Pro Val Ser Ile Pro Trp Met Pro Gly Val Leu Val Arg  
           35                  40                  45  
 Phe Phe Thr Leu Leu Xaa  
           50

<210> 126  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (44)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (82)  
 <223> Xaa equals stop translation

<400> 126  
 Met Arg Met Arg Val Ala Val Ala Pro Arg Pro His Gln His Leu Val  
           1                  5                  10                  15  
 Val Ser Val Ser Trp Ile Leu Ala Ile Leu Ile Ser Val Ser Gly Tyr  
                   20                  25                  30  
 His Cys Phe His Leu Gln Phe Ser Tyr Met Val Xaa Asn Ile Phe Pro  
           35                  40                  45  
 His Val Tyr Leu Ser Ser Ala Tyr Leu Leu Arg Pro Val Ile Cys Ser  
           50                  55                  60  
 Asp Leu Leu Pro Val Phe Val Cys Leu His Val Cys Leu Cys Leu Ile  
           65                  70                  75                  80  
 Phe Xaa



<210> 127  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals stop translation

<400> 127  
 Met Gly Trp Glu Ala Ala Leu Ala Leu Val Ser Ala Val Phe Phe  
           1                  5                  10                  15  
 Pro Trp Cys Thr Ile Gln Arg Pro Asp Val Gly Thr Thr Ser Pro Gly  
                   20                  25                  30  
 Gly Leu Glu Arg Arg Ser Lys Gly Phe Xaa  
           35                  40

<210> 128  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals stop translation

<400> 128  
 Met Thr Phe Met Ile Leu Lys Phe Phe Phe Leu Cys Gly Phe Val Leu  
           1                  5                  10                  15  
 Asn Arg Leu Ile Ala Arg Gln Leu Ala Lys Ile His Ala Ile His Ala  
                   20                  25                  30  
 His Asn Gly Trp Ile Pro Lys Ser Asn Leu Trp Leu Lys Met Gly Lys  
           35                  40                  45  
 Tyr Phe Ser Leu Ile Pro Thr Gly Phe Ala Asp Glu Asp Ile Asn Lys  
           50                  55                  60  
 Arg Xaa  
       65

<210> 129  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 129

Met Ile Val Asn His Phe Ser Phe Leu Phe Cys Trp Ile Val Phe Cys  
1 5 10 15

Phe Leu Leu Gln His Ser Cys Phe Cys Cys Ala Tyr Phe Trp Ser Phe  
20 25 30

Asp Ser Leu Cys His Cys Phe Leu Ser His Thr Pro Leu Arg Phe Thr  
35 40 45

Gln Xaa  
50

&lt;210&gt; 130

&lt;211&gt; 227

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (227)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 130

Met Glu Thr Val Val Ile Val Ala Ile Gly Val Leu Ala Thr Ile Phe  
1 5 10 15

Leu Ala Ser Phe Ala Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys  
20 25 30

Arg Pro Arg Asp Leu Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp  
35 40 45

Leu Ile Gly Ala Met Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu  
50 55 60

Asp Asp Val Val Ile Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn  
65 70 75 80

Glu Asp Trp Ile Glu Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala  
85 90 95

Ile Leu Lys Ile Cys His Thr Leu Thr Glu Lys Leu Val Ala Met Thr  
100 105 110

Met Gly Ser Gly Ala Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile  
115 120 125

Ile Val Val Ala Lys Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys  
 130 135 140

Ser Met Tyr Pro Pro Leu Asp Pro Lys Leu Leu Asp Ala Arg Thr Thr  
 145 150 155 160

Ala Leu Leu Leu Ser Val Ser His Leu Val Leu Val Thr Arg Asn Ala  
 165 170 175

Cys His Leu Thr Gly Gly Leu Asp Trp Ile Asp Gln Ser Leu Ser Ala  
 180 185 190

Ala Glu Glu His Leu Glu Val Leu Arg Glu Ala Ala Leu Ala Ser Glu  
 195 200 205

Pro Asp Lys Gly Leu Pro Gly Pro Glu Gly Phe Leu Gln Glu Gln Ser  
 210 215 220

Ala Ile Xaa  
 225

<210> 131  
 <211> 118  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (118)  
 <223> Xaa equals stop translation

<400> 131  
 Met Gln Arg Ile Ala Ser Leu Leu Thr Leu Leu Thr Gln Leu Thr Leu  
 1 5 10 15

Ala Ala Gly Ser Thr Pro Ala Glu Thr Ile Ser Asp Ser Ala Glu Ala  
 20 25 30

Ser Leu Ser Ala Thr Pro Ser Leu Val Thr Trp Thr Gln Val Ser Gly  
 35 40 45

Leu Gln Pro Leu Val Glu Pro Cys Leu Arg Gln Thr Leu Lys Leu Leu  
 50 55 60

Ser Arg Pro Glu Met Trp Arg Ala Val Gly Pro Val Pro Val Ala Cys  
 65 70 75 80

Leu Leu Phe Leu Gly Ala Tyr Tyr Gln Ala Trp Ser Gln Gln Pro Ser  
 85 90 95

Ser Cys Pro Glu Asp Trp Leu Gln Asp Met Glu Arg Leu Ser Glu Ser  
 100 105 110

Cys Cys Cys His Cys Xaa

115

&lt;210&gt; 132

&lt;211&gt; 306

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (180)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (197)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (306)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 132

Met	Ser	Glu	Asp	Arg	Pro	Met	Leu	Gln	Phe	Leu	Leu	His	Thr	Ser	Phe
1				5					10					15	

Leu	Ser	Pro	Leu	Phe	Ile	Leu	Trp	Leu	Trp	Thr	Lys	Pro	Ile	Ala	Arg
			20					25						30	

Asp	Phe	Leu	His	Gln	Pro	Pro	Phe	Gly	Glu	Thr	Arg	Phe	Ser	Leu	Leu
		35					40					45			

Ser	Asp	Ser	Ala	Phe	Asp	Ser	Gly	Arg	Leu	Trp	Leu	Leu	Val	Val	Leu
	50					55					60				

Cys	Leu	Leu	Arg	Leu	Ala	Val	Thr	Arg	Pro	His	Leu	Gln	Ala	Tyr	Leu
65					70					75					80

Cys	Leu	Ala	Lys	Ala	Arg	Val	Glu	Gln	Leu	Arg	Arg	Glu	Ala	Gly	Arg
				85					90					95	

Ile	Glu	Ala	Arg	Glu	Ile	Gln	Gln	Arg	Val	Val	Arg	Val	Tyr	Cys	Tyr
			100					105					110		

Val	Thr	Val	Val	Ser	Leu	Gln	Tyr	Leu	Thr	Pro	Leu	Ile	Leu	Thr	Leu
		115					120					125			

Asn	Cys	Thr	Leu	Leu	Leu	Lys	Thr	Leu	Gly	Gly	Tyr	Ser	Trp	Gly	Leu
		130				135					140				

Gly	Pro	Ala	Pro	Leu	Leu	Ser	Pro	Arg	Pro	Ile	Leu	Ser	Gln	Arg	Cys
145					150					155					160

Pro	His	Arg	Leu	Trp	Gly	Gly	Arg	Ser	Pro	Ala	Asp	Cys	Ser	Ala	Asp
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

[illegible]

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<210> 133
<211> 45
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (45)
<223> Xaa equals stop translation
```

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<400> 133
Met Ser Tyr Ser Leu Phe Leu Ala Leu Leu Ser Phe Ala Ser Ala Ile
 1             5             10             15
Leu Phe Val Ala Gly Thr Ile Ala Gly Thr Gly Gly Leu Ser Phe His
      20             25             30
Gly Ile Ala Thr Ile Phe Val Leu Thr Gly Lys Trp Xaa
      35             40             45

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<210> 134
<211> 44
<212> PRT
<213> Homo sapiens
```

<220>  
<221> SITE  
<222> (6)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 134  
Met Gly Arg Leu Gly Xaa Gln Cys Leu Leu Phe Leu Ala Phe Lys Ala  
1 5 10 15  
Ile Ser Gly Val Phe Phe Leu Phe Trp Arg Pro Ala Asp Ser Thr Glu  
20 25 30  
Arg Asn Thr Gln Ser Trp Asp Phe Pro Pro Leu Xaa  
35 40

<210> 135  
<211> 50  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (50)  
<223> Xaa equals stop translation

<400> 135  
Met Gly Val Gly Val Leu Arg Ile Leu Leu Ser Cys Leu Gly Glu Ala  
1 5 10 15  
Ala Pro Lys Ser Ala Gly Thr Ser Leu Glu Ser Ala Lys Glu Cys Trp  
20 25 30  
Ser Ala Ala Thr Leu Leu Val Leu Cys Val Leu Cys Gln Leu Gln His  
35 40 45  
Gly Xaa  
50

<210> 136  
<211> 81  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (81)  
<223> Xaa equals stop translation

&lt;400&gt; 136

Met Glu Ser Leu Pro Glu Asn Lys Pro Leu Val Trp Ser Leu Ala Val  
 1 5 10 15  
 Ser Leu Leu Ala Ile Ile Gly Leu Leu Leu Gly Ser Ser Pro Asp Phe  
 20 25 30  
 Asn Ser Gln Phe Gly Leu Val Asp Ile Pro Val Glu Phe Lys Leu Val  
 35 40 45  
 Ile Ala Gln Val Leu Leu Leu Asp Phe Cys Leu Ala Leu Leu Ala Asp  
 50 55 60  
 Arg Val Leu Gln Phe Phe Leu Gly Thr Pro Lys Leu Lys Val Pro Ser  
 65 70 75 80

Xaa

&lt;210&gt; 137

&lt;211&gt; 277

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (94)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (103)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (277)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 137

Met Ile His Val Asn Arg Asn Ile Met Asp Phe Lys Leu Phe Leu Val  
 1 5 10 15  
 Phe Val Ala Gly Val Phe Leu Phe Phe Tyr Ala Arg Thr Leu Glu Ser  
 20 25 30  
 Lys Pro Tyr Phe Leu Leu Leu Leu Gly Asn Cys Ala Arg Cys Ser Asn  
 35 40 45  
 Asp Ile Val Phe Val Leu Leu Leu Val Lys Arg Phe Ile Arg Ser Ile  
 50 55 60  
 Ala Pro Phe Gly Ala Leu Met Val Gly Cys Trp Phe Ala Ser Val Tyr

65		70		75		80
Ile Val Cys Gln Leu Met Glu Asp Leu Lys Trp Leu Trp Xaa Glu Asn						
		85		90		95
Arg Ile Tyr Val Ser Gly Xaa Val Leu Ile Val Gly Phe Phe Ser Phe						
		100		105		110
Val Val Cys Tyr Lys His Gly Pro Leu Ala His Asp Arg Ser Arg Ser						
		115		120		125
Leu Leu Met Trp Met Leu Arg Leu Leu Ser Leu Val Leu Val Tyr Ala						
		130		135		140
Gly Val Ala Val Pro Gln Phe Ala Tyr Ala Ala Ile Ile Leu Leu Met						
		145		150		155
Ser Ser Trp Ser Leu His Tyr Pro Leu Arg Ala Cys Ser Tyr Met Arg						
		165		170		175
Trp Lys Met Glu Gln Trp Phe Thr Ser Lys Glu Leu Val Val Lys Tyr						
		180		185		190
Leu Thr Glu Asp Glu Tyr Arg Glu Gln Ala Asp Ala Glu Thr Asn Ser						
		195		200		205
Ala Leu Glu Glu Leu Arg Arg Ala Cys Arg Lys Pro Asp Phe Pro Ser						
		210		215		220
Trp Leu Val Val Ser Arg Leu His Thr Pro Ser Lys Phe Ala Asp Phe						
		225		230		235
Val Leu Gly Gly Ser His Leu Ser Pro Glu Glu Ile Ser Leu His Glu						
		245		250		255
Glu Gln Tyr Gly Leu Gly Gly Ala Phe Leu Glu Glu Gln Leu Phe Asn						
		260		265		270
Pro Ser Thr Ala Xaa						
		275				

&lt;210&gt; 138

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 138

Met Cys Gln Thr Leu Pro Ala Arg Leu Arg Ala Gln Cys Ile Ser Ser
1 5 10 15



Leu Leu Phe Leu Leu Met Gly Leu Leu Ala Met Thr Gly Glu Arg Asn  
20 25 30  
Gln Gly Thr His Tyr Tyr Glu Phe Ser Gly Phe Ile Phe Lys Ser Gln  
35 40 45  
Met Met Trp Ser Ile Lys Pro Asn Xaa  
50 55

```
<210> 139
<211> 71
<212> PRT
<213> Homo sapiens
```

```
<220>  
<221> SITE  
<222> (71)  
<223> Xaa equals stop translation
```

```

<400> 139
Met Tyr Leu Trp Phe Ser Phe Ser Thr Val Gly Leu Cys Gly Cys Cys
  1                               10                      15

Leu Leu Tyr Arg Ala Cys Gly Phe Ile Trp Tyr Leu Leu Leu Leu Gly
      20                      25                      30

His Ser Ser Thr Asn Ser Leu Gln Asp Gly Gly Ala Glu Arg Pro Glu
      35                      40                      45

His Pro Trp Ala His Val Arg Tyr Ser Cys Arg Arg Glu Leu Ser Phe
      50                      55                      60

Trp Phe Tyr Val Phe Asn Xaa
  65                      70

```

```
<210> 140
<211> 63
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (63)
<223> Xaa equals stop translation
```

```

<400> 140
Met Glu Pro Glu Ser Trp Ala Leu Cys Leu Leu Leu Phe Leu Gly Thr
  1                      5                      10                      15
Ala Leu Gly Tyr Pro Pro Leu Pro Arg His Ser Ser Lys Cys Glu Ile
          20                      25                      30

```

Leu Glu Val Arg Leu His Leu Leu Pro Leu Leu Ile Asn Ile Gly Met  
                   35                                  40                                  45

Met Ser Pro Val Ala Ser Pro Phe Val Cys Ser Ile Thr Gly Xaa  
           50                                  55                                  60

<210> 141  
 <211> 89  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (89)  
 <223> Xaa equals stop translation

<400> 141  
 Met Leu Phe Leu Ser Ala Ser Ile Cys Thr Ser Ala Leu Phe Leu Cys  
       1                                  5                                  10                                  15

Leu Ser Arg Leu Thr Ile Ser Ala Pro His Pro Ala Trp Trp Gly Arg  
                   20                                  25                                  30

Met Pro Thr His Thr Ser Pro Gly His Leu Leu Glu Leu Gln Pro Arg  
                   35                                  40                                  45

Gly Met Thr Glu Ser Ile Leu Phe Ser Ile Ser Ala Leu Val Ser Asn  
           50                                  55                                  60

Ser Trp Gly Lys Met Thr Gln Leu Thr Ser Gly Ser His Ser Trp Ser  
       65                                  70                                  75                                  80

Ser Gly Leu Gln Asn Phe Gln Ala Xaa  
                                   85

<210> 142  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals stop translation

<400> 142  
 Met Arg Pro Val Cys Ser Leu Gly Trp Ala Gly Trp Pro Gly Leu Val  
       1                                  5                                  10                                  15

Cys Gly Leu Arg Ala Leu Leu Gly Pro Ser Leu Phe Pro Val Thr Phe  
                   20                                  25                                  30

Gly Ala Thr Glu Ala Val His Ser Leu Asp Val Cys Ser Xaa

35

40

45

&lt;210&gt; 143

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 143

Met Val Asn Glu Lys Glu Ala Arg Thr Gly Ser Pro Lys Ser Trp Leu  
 1 5 10 15

Leu Cys Leu Ala Leu Leu Leu Ile Lys Tyr Val Thr Phe Cys Lys Pro  
 20 25 30

Tyr Leu Thr Lys Pro Tyr Phe Leu His Leu Ser Val Leu Asp Gln Leu  
 35 40 45

Ser Pro Gly Thr Pro Leu Asp Xaa  
 50 55

&lt;210&gt; 144

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (77)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 144

Met Phe Ile Ala Ile Tyr Phe Lys Ala Phe His Gly Ser Phe Gln Leu  
 1 5 10 15

Cys Thr Trp Leu Val Ile Met Ile Val Ile Leu Gly Gln Ser Phe Ser  
 20 25 30

Ala Leu Ala Leu Leu Thr Phe Trp Leu Ile Leu Cys Cys Arg Gly Cys  
 35 40 45

Pro Val His Cys Arg Val Phe Ser Ser Ile Pro Asp Leu Tyr Leu Leu  
 50 55 60

Asn Ala Arg Ser Asn Thr Val Pro Pro Ala Gln Leu Xaa  
 65 70 75

&lt;210&gt; 145

<211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 145  
 Met Phe Phe Leu Ser Met Phe Leu His Ile Val Leu Leu His Cys Gly  
           1                  5                  10                  15  
 Asn Ser Phe Tyr Lys Ile Cys His Ser Trp Asp Tyr Ala Ala Leu Gln  
                   20                  25                  30  
 Glu Ser Thr Arg Phe Tyr Ser Asn Ser Tyr Xaa  
                   35                  40

<210> 146  
 <211> 102  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (67)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (102)  
 <223> Xaa equals stop translation

<400> 146  
 Met Glu Leu Glu Arg Cys Ser Val Val Leu Cys Ile Leu Ala Asn Leu  
           1                  5                  10                  15  
 Ala Val Leu Arg Ala Leu Phe Leu Pro Cys Ile Ile Phe His Cys Val  
                   20                  25                  30  
 Ser Asp Ser Arg Ser Val Asn Arg Glu Thr Lys Val Lys Phe Val His  
           35                  40                  45  
 Thr Ser Val His Gly Val Gly His Ser Phe Val Gln Ser Ala Phe Lys  
           50                  55                  60  
 Ala Phe Xaa Leu Val Pro Pro Glu Ala Val Pro Glu Gln Lys Asp Pro  
           65                  70                  75                  80  
 Asp Pro Glu Phe Pro Thr Val Lys Tyr Pro Asn Pro Glu Glu Gly Lys  
                   85                  90                  95  
 Gly Val Leu Val Thr Xaa

100

&lt;210&gt; 147

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (134)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 147

Met	Arg	Val	Pro	Leu	Val	Leu	Ser	Trp	Ala	Phe	Val	Leu	Val	Gly	Phe
1				5					10					15	

Ser	Gly	Val	Tyr	Leu	Ala	Ser	Glu	Ser	Phe	Trp	Phe	Pro	Pro	Ser	Leu
			20					25					30		

Cys	Asp	Leu	Thr	Ser	Pro	Pro	Gly	Leu	His	Leu	Trp	Lys	Phe	Ile	Arg
		35					40					45			

Asp	Leu	Val	Ser	Met	Glu	Glu	Leu	Thr	Asp	Ser	Ala	Arg	Glu	Met	Gly
	50					55					60				

Tyr	Trp	Met	Met	Val	Phe	Ser	Leu	Lys	Ala	Met	Phe	Pro	Val	Ser	Ser
65					70					75					80

Gly	Cys	Phe	Gln	Glu	Arg	Gln	Glu	Thr	Asn	Lys	Ser	Leu	Thr	Leu	Leu
			85						90					95	

Arg	Cys	Ser	Gln	Arg	Asp	Thr	Ser	Pro	Leu	Met	Asp	Gly	Gln	Thr	Trp
		100						105					110		

Ala	Arg	Val	Arg	Val	Thr	Lys	Pro	Pro	Thr	Thr	Ala	Thr	Ala	Ala	Tyr
		115					120					125			

Asn	Arg	His	Ile	Arg	Xaa
		130			

&lt;210&gt; 148

&lt;211&gt; 50

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 148

Met	Lys	Ser	Leu	Phe	Cys	Ile	Tyr	Phe	Leu	Arg	Trp	Pro	Met	Gly	Leu
1				5					10					15	

Ser Trp Gly Glu Thr Phe Ile Leu Leu Arg Asp Ser Leu Ala Ile Asn  
20 25 30  
Phe Gln Ser Phe Ser Lys Ala Ala Ser Gly Asp Ile Phe Gly Cys His  
35 40 45  
Asp Xaa  
50

<210> 149  
<211> 64  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (6)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (64)  
<223> Xaa equals stop translation

<400> 149  
Met Ser Cys Gly Leu Xaa Phe Gly Pro Trp Phe Val Pro Met Leu Leu  
1 5 10 15  
Met Ser His Ser Leu Leu Pro Ser Trp Ser Gly Leu Trp Val Thr Thr  
20 25 30  
Trp Asn Gly Ser Ser Gly Glu Arg Thr Pro Ser Pro Trp Arg Arg Lys  
35 40 45  
Arg Ala Ser Gln Ser Ala Gly Arg Ile Ala Ser Trp Met Ser Phe Xaa  
50 55 60

<210> 150  
<211> 75  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (59)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE

&lt;222&gt; (75)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 150

Met	Leu	Ser	Ser	Pro	Asn	Leu	Ala	Ala	Ser	Leu	Leu	Cys	Leu	Trp	His
1				5					10					15	

Ser	Gly	Ser	Ala	Thr	Asn	Trp	Ala	Pro	Pro	Cys	Ala	Gly	Met	Trp	Ala
			20					25					30		

Ser	Arg	Cys	Gly	Trp	Lys	Val	Ser	Pro	His	Pro	Glu	Ala	Gly	Pro	Cys
		35					40					45			

Ser	Ser	Ala	Leu	Trp	Val	Ser	Cys	Cys	Val	Xaa	Ala	Glu	Gln	Pro	Gln
	50					55				60					

Pro	Gly	Gly	Arg	Glu	Pro	Arg	His	Arg	Gly	Xaa
65					70					75

&lt;210&gt; 151

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 151

Met	Pro	His	Ile	Ser	Phe	Cys	Leu	Gly	Thr	Pro	Tyr	Val	Val	Ala	Val
1				5					10					15	

Tyr	Leu	Pro	Ala	Trp	Ile	Val	Met	Leu	Leu	Leu	Pro	Gly	Val	Arg	Pro
			20				25						30		

Tyr	Ser	Ser	Leu	Gln	Ala	Leu	Lys	His	Pro	Ser	Cys	Ser	Ser	Ser	Ser
		35					40					45			

Val	Cys	Ala	Pro	Tyr	Met	Xaa
50					55	

&lt;210&gt; 152

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 152

92

Met Gly Leu Asn Ile Ser Pro Trp Cys Phe Leu Ala Ile Leu Thr Cys  
1 5 10 15  
Ala Ile Ser Ala Ala Phe Ile Ser Val Gly Val Val Cys Trp Leu Leu  
20 25 30  
Phe Leu Ile Ser His Arg Ser Ser Lys Asn Leu Arg Lys Ser Arg Val  
35 40 45  
Arg Gly Val Trp Glu Asn Glu Glu Ile Xaa  
50 55

<210> 153  
<211> 53  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (53)  
<223> Xaa equals stop translation

<400> 153  
Met Ala Tyr Val Leu Ala Val Leu Cys Phe Lys Ser Leu Trp Ala Leu  
1 5 10 15  
Phe Lys Pro Asn Lys Gln Leu Ile Glu Phe Leu Leu Met Val Lys Val  
20 25 30  
Val Lys Ile Pro Leu Cys Tyr Leu Arg Gln Leu Leu Gly Gly Ile Lys  
35 40 45  
Thr Pro Arg Val Xaa  
50

<210> 154  
<211> 51  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (51)  
<223> Xaa equals stop translation

<400> 154  
Met Asp Gly Gly Pro Gly Ala Phe Ser Arg Ala Trp Val Leu Gln Ile  
1 5 10 15  
Pro Trp Leu Leu Leu Ser Gly Gly Asn Phe Ala Leu Cys Glu Pro Arg  
20 25 30  
Pro Cys Pro Ser Ala Gly His Pro Trp Gln Glu Ala Gly Leu Pro Ser



35

40

45

Ser Pro Xaa  
50

&lt;210&gt; 155

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (67)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 155

Met Pro Phe Leu Ser Val Trp Phe Phe Asn Leu Gly Leu Ile Phe Gly  
1 5 10 15

Val Glu Ser Phe Val Leu Arg Ala Val Leu Phe Ile Ala Gly Cys Ser  
20 25 30

Ala Thr Ser Gln Met Glu Ala Ala Ser Pro Tyr Pro Ala Val Thr Lys  
35 40 45

Arg Lys Lys Asn Val Ser Xaa His Cys Gln Ile Ser Ser Gly Gly Ala  
50 55 60

Pro Gly Xaa  
65

&lt;210&gt; 156

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 156

Met Leu Leu Lys Arg Asn Leu Leu Ile Leu Ile Leu Phe Leu Val Thr  
1 5 10 15

Cys Phe Asn Phe Val Ser Phe Phe Phe Phe Pro Trp Lys Leu Leu Gly  
20 25 30

Ser Pro Phe Tyr Pro Cys Ser Leu Arg Ser Asp Asn Asp Gly Cys Val  
                   35                                  40                                  45

Xaa

<210> 157

<211> 61

<212> PRT

<213> Homo sapiens

<400> 157

Met Gly Ser Phe Leu His Pro Gln Trp His Leu Leu Ile Thr Phe Cys  
   1                                  5                                  10                                  15

Ala Val Leu Gly Lys Gly Leu His Ser Asp Pro Ser Arg Pro Phe Glu  
                   20                                  25                                  30

His Gly Gly Ala Leu Gly Lys Val Pro Arg Gly Arg Ser Thr Leu Leu  
                   35                                  40                                  45

Ser Lys Glu Val Leu Leu Lys Lys Lys Lys Lys Lys Arg  
           50                                  55                                  60

<210> 158

<211> 118

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (113)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (118)

<223> Xaa equals stop translation

<400> 158

Met Leu Leu Trp Trp Gln Cys Leu Cys Cys His Ala Val Leu Glu Pro  
   1                                  5                                  10                                  15

Ala Ala Thr Ala Met Pro Glu Asp Ala Ala Pro Ser Ser Leu Pro Val  
                   20                                  25                                  30

Pro Pro Asn Met Thr Ser Ser Arg Phe His Tyr Phe Trp Thr Leu Leu  
                   35                                  40                                  45

Gln Ile Lys Leu Thr Gln Phe Tyr Ser Lys Pro Arg Ser Leu Ser Ala  
           50                                  55                                  60

Thr Pro Glu Lys Asn Ile Gly Leu Gln Glu Pro Glu Arg Arg Glu Arg

```
<210> 159
<211> 151
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (151)
<223> Xaa equals stop translation
```

```

<400> 159
Met Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val
  1             5             10             15

Phe Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu
      20             25             30

Leu Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr
      35             40             45

Val Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr
  50             55             60

Pro Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly
  65             70             75             80

Tyr Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val
      85             90             95

Tyr Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe
      100             105             110

Gly Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val
      115             120             125

Leu Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys
      130             135             140

Glu Lys Pro Lys Leu Glu Xaa
145             150

```

<210> 160

<211> 92  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (92)  
<223> Xaa equals stop translation

<400> 160  
Met Gly Asp Lys Leu Gly Met Ala Arg Ala Pro Ser Val Ala Leu Ala  
1 5 10 15  
Gln Leu Trp Leu Ile Cys Leu Cys Pro Glu Ser Leu Ala Ser Phe Val  
20 25 30  
Gln Ala Val Pro Trp Lys Val Leu Gln Pro Ser Ser Asn Arg Ser Thr  
35 40 45  
Asp Cys Ser Pro His Met Arg Pro Thr Cys Glu Thr Leu Gly Ser Arg  
50 55 60  
Lys Ala Gln Asp Leu Val Leu Asp Thr Met Cys Leu Ser Thr Asp Asp  
65 70 75 80  
Cys Gln Gly Leu Ile Cys Arg Gly His Arg Ser Xaa  
85 90

<210> 161  
<211> 42  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (42)  
<223> Xaa equals stop translation

<400> 161  
Met Gln Val Ala Cys Val Met Lys Val Ser Ala Gln Trp Val Cys Phe  
1 5 10 15  
Phe Val Val Phe Ser Pro Leu Cys Ser Ser Val Lys Cys Ala Ser Ser  
20 25 30  
Gly Gln Asn Arg Gly Arg Gly Asp Gln Xaa  
35 40

<210> 162  
<211> 78  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (78)  
<223> Xaa equals stop translation  
  
<400> 162  
Met Met Leu Gln Ile Ile His Leu Asn Thr Leu Ile Lys Phe Phe Gln  
1 5 10 15  
Cys Leu Lys Leu Phe Leu His Gly Thr Ala Gly Ser Gly Gln Lys Cys  
20 25 30  
Leu Ala Tyr Lys Phe Ser Gln Phe Pro Ser Ile Ile Pro Ala Ala His  
35 40 45  
Lys Lys Val His His Leu Leu Ser Pro Lys Cys Leu Pro Thr Glu Cys  
50 55 60  
Ser Gln Ala Asp Asn Ser Ser Trp Asp Ser Ala Val Trp Xaa  
65 70 75

<210> 163  
<211> 55  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (55)  
<223> Xaa equals stop translation  
  
<400> 163  
Met Lys Arg Leu Trp Cys Leu Ser Trp Val Pro Gly Leu Gln Gly Ser  
1 5 10 15  
Pro Ser Val Leu Ser Ser Val Phe Phe Ser Val Phe Lys Pro Gln Leu  
20 25 30  
His Trp Thr Cys Ser Gln Val Ser Ser His Trp His Pro Pro Cys Leu  
35 40 45  
Phe Ile Leu Phe Ser Gly Xaa  
50 55

<210> 164  
<211> 90  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (90)  
<223> Xaa equals stop translation

&lt;400&gt; 164

Met Lys Phe Leu Leu Ala Ala Leu Val Leu Ser Leu Ile Leu Pro Arg  
 1 5 10 15

Ser Ser Gln Tyr Ile Lys Trp Ile Val Ser Ala Gly Leu Ala Gln Val  
 20 25 30

Ser Glu Phe Ser Phe Val Leu Gly Ser Arg Ala Arg Arg Ala Gly Val  
 35 40 45

Ile Ser Arg Glu Val Tyr Leu Leu Ile Leu Ser Val Thr Thr Leu Ser  
 50 55 60

Leu Leu Leu Ala Pro Val Leu Trp Arg Ala Ala Ile Thr Arg Cys Val  
 65 70 75 80

Pro Arg Pro Glu Arg Arg Ser Ser Leu Xaa  
 85 90

&lt;210&gt; 165

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (45)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 165

Met Phe Val Trp His Leu Lys Val Met Val Met Phe Ile Ile Leu Tyr  
 1 5 10 15

Phe Ala Tyr Cys Glu Ser Asn Phe His Ser Val Leu Ser Val Ser Lys  
 20 25 30

Pro Leu Leu Lys Ile Leu Phe Leu Pro Arg Asn Leu Xaa  
 35 40 45

&lt;210&gt; 166

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (45)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 166

Met Thr Pro Gly Cys Ser Val Pro Phe Leu Leu Cys Trp Leu Phe Ala  
 1 5 10 15

Leu Met Met Gln Glu Lys Trp Gly Gly Val Lys Ser Leu Val Ser Tyr  
                   20                                  25                                  30

His Tyr Ser Arg Gln Trp His Gln Thr Val Val Val Xaa  
           35                                  40                                  45

<210> 167  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals stop translation

<400> 167  
 Met Ser Ile Ala Leu Arg Ile Asn Arg Leu His Phe Trp Val Leu Leu  
   1                                  5                                  10                                  15

Phe Phe Phe Phe Phe Ala Gln Leu Ser Leu Ser Val Asp Leu His Gly  
                   20                                  25                                  30

Thr Ser Tyr Ser Leu Lys Ser Leu Ser Tyr Leu Thr Ile Phe Leu Asp  
           35                                  40                                  45

Leu Glu Lys Leu Asp Val Gly Pro Tyr Glu Lys Ile Ile Arg Asn Gln  
           50                                  55                                  60

Ile Xaa  
   65

<210> 168  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals stop translation

<400> 168  
 Met Gln Leu Thr Leu Gly Gly Ala Ala Val Gly Ala Gly Ala Val Leu  
   1                                  5                                  10                                  15

Ala Ala Ser Leu Leu Trp Ala Cys Ala Val Gly Leu Tyr Met Gly Gln  
           20                                  25                                  30

Leu Glu Leu Asp Val Glu Leu Val Pro Glu Asp Asp Gly Thr Ala Ser  
           35                                  40                                  45

100

Ala Glu Gly Pro Asp Glu Ala Gly Arg Pro Pro Pro Glu Xaa  
 50 55 60

&lt;210&gt; 169

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 169

Met His Thr Ala Lys Met Ser Leu Leu Asn Ser Val Cys Leu Leu Val  
 1 5 10 15

Leu Ser Ile Trp Tyr Val Val Lys Phe Pro Met Met Arg Asp Ser Thr  
 20 25 30

Ile Asn Val Pro Tyr Leu Leu Arg Leu Lys Ala Ile Thr Thr Xaa  
 35 40 45

&lt;210&gt; 170

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (106)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 170

Met Ser Gly Leu Ala Ala Ala Ala His Val Phe Arg Val Cys Leu Phe  
 1 5 10 15

Pro Leu Ser Trp Gly Ser Ser Lys Thr Thr Phe Ile His Gly Leu Ser  
 20 25 30

Ser Tyr Ile Ala Thr Pro Val Leu Asn Ser Ile Phe Ser Ser Trp Lys  
 35 40 45

Ser Arg Arg Lys Asp Thr Trp Thr Cys Leu Leu His Arg Leu Ser Ala  
 50 55 60

Phe Pro Ile Ser Xaa Arg Arg Arg Asn Phe Ala Leu Phe Ser His Ser  
 65 70 75 80



Cys Val Cys Ile Arg Ser Ser Ser Asp Asp Val Gly Pro Thr Met Tyr  
                             85                            90                            95

Ser Phe Ser Val Pro Cys Arg Val Lys Xaa  
                             100                            105

<210> 171  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation

<400> 171  
 Met His Leu Leu Thr Leu Phe Ser Ser Gly Leu Ile Phe Leu Gly Cys  
       1                            5                            10                            15

Ser Thr Pro Leu Ser Phe Cys Asp Cys Leu Pro Ile Leu Leu Leu Trp  
                             20                            25                            30

Leu Glu Phe Pro Val Glu Thr Ser Gly Val Cys Ser Xaa  
                             35                            40                            45

<210> 172  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (47)  
 <223> Xaa equals stop translation

<400> 172  
 Met Ile Leu Lys His Tyr Ile Leu Thr Phe Ile Phe Leu Phe Ile Phe  
       1                            5                            10                            15

Leu Phe Phe Met Leu Asn Ile Leu His Ser Asn Ser Asn Leu Ile Asp  
                             20                            25                            30

Leu Leu Lys Gly Asn Ile Arg Phe Arg Leu Leu Asn Ser Met Xaa  
                             35                            40                            45

<210> 173  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

102

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 173

Met Ala Thr Leu Gln Ile Thr Thr Ala Met Lys Ile Thr Met Met Ile  
 1 5 10 15

Thr Met Val Met Ile Ile Thr Thr Ile Val Glu Ala Met Lys Ile Pro  
 20 25 30

Thr Thr Ala Met Met Met Ala Met Gln Xaa  
 35 40

&lt;210&gt; 174

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 174

Met Glu Met Leu Ser Ser Lys Trp Ser Lys Arg Val Ala Ala Ser Leu  
 1 5 10 15

Ala His Leu Ile Ser Leu Phe Ile Gly Leu Leu Phe Leu Leu Leu Gly  
 20 25 30

Ser Ser Val Tyr Pro Gly Thr Glu Thr Leu Phe Pro Lys Ser Xaa  
 35 40 45

&lt;210&gt; 175

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 175

Met Trp Pro Ser Leu Gly Arg Cys Cys Leu Phe Phe Cys Leu Leu Thr  
 1 5 10 15

Asn Leu Thr Ser Cys His Thr Ser Gln Ile Thr Leu Cys Ser Arg Glu  
 20 25 30

Thr Cys Val Trp Ser Arg Thr Thr Xaa

35

40

&lt;210&gt; 176

&lt;211&gt; 53

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 176

Met	Tyr	Leu	Met	Ser	Phe	Ser	Ile	His	Phe	Val	Lys	Ile	Ile	Cys	Met
1				5					10					15	

Cys	Thr	Ile	Leu	Val	Leu	Ser	Pro	Pro	Val	Leu	Leu	Lys	Tyr	Gln	Asp
			20					25					30		

Ser	Thr	Pro	Arg	Pro	Leu	Trp	Ser	Gln	Cys	Lys	Ile	Pro	Ile	Asn	Tyr
		35					40					45			

Leu	Lys	Gly	Lys	Xaa
				50

&lt;210&gt; 177

&lt;211&gt; 250

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (250)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 177

Met	Arg	Gly	Pro	Ser	Trp	Ser	Arg	Pro	Arg	Pro	Leu	Leu	Leu	Leu	Leu
1				5					10					15	

Leu	Leu	Leu	Ser	Pro	Trp	Pro	Val	Trp	Ala	Gln	Val	Ser	Ala	Arg	Ala
			20					25					30		

Ser	Pro	Ser	Gly	Ser	Leu	Gly	Ala	Pro	Asp	Cys	Pro	Glu	Val	Cys	Thr
		35					40					45			

Cys	Val	Pro	Gly	Gly	Leu	Pro	Ala	Val	Gly	Thr	Leu	Ala	Ala	Arg	Arg
	50					55					60				

Ala	Pro	Gly	Pro	Glu	Pro	Ala	Pro	Ala	Arg	Ala	Ala	Ala	Gly	Pro	Gln
65					70				75					80	

Pro	Arg	Pro	Cys	Ala	Ala	Ala	Arg	Cys	Leu	Arg	Gly	Ser	Gly	Arg	Ala
				85					90					95	

104

Thr Ala Pro Gly Pro Ala Arg Glu Arg Ala Ala Leu Gly Ala Cys Ala  
                   100                  105                  110  
 Ser Leu Leu Gly Pro Gly Arg Ala Ala Ala Gly Pro Glu Arg Gln  
                   115                  120                  125  
 Pro Ala Gly Ser Thr Gly Thr Arg Asp Phe Arg Ala Ala Ala Arg Ala  
                   130                  135                  140  
 Ala Gln Pro Leu Ile Gly Arg Gln Pro Ala Gly Ala Pro Gly Ala Arg  
                   145                  150                  155                  160  
 Gly Ala Arg Arg Ala Pro Ala Ala Ala Leu Thr Gln Pro Ala Gly Gln  
                   165                  170                  175  
 Arg Ala Gly Gly Thr Arg Ala Gly Ala Ala Gly Pro Pro Ala Arg Ser  
                   180                  185                  190  
 Arg Arg Ala Ala Pro Ala Arg Gln Pro Leu Gly Leu Arg Val Arg Ala  
                   195                  200                  205  
 Ala Pro Ala Leu Arg Leu Ala Ala Pro Ala Pro Ala Ala Arg Val Arg  
                   210                  215                  220  
 Gly Arg Asp Gly Ala Leu Arg Val Ala Gly Thr Pro Asp Ala Gln Pro  
                   225                  230                  235                  240  
 Pro Asp Cys Leu Phe Arg Arg Arg Leu Xaa  
                   245                  250

&lt;210&gt; 178

&lt;211&gt; 148

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (148)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 178

Met Leu Ala Gly Ala Gly Arg Pro Gly Leu Pro Gln Gly Arg His Leu  
   1                  5                  10                  15  
 Cys Trp Leu Leu Cys Ala Phe Thr Leu Lys Leu Cys Gln Ala Glu Ala  
                   20                  25                  30  
 Pro Val Gln Glu Glu Lys Leu Ser Ala Ser Thr Ser Asn Leu Pro Cys  
                   35                  40                  45  
 Trp Leu Val Glu Glu Phe Val Val Ala Glu Glu Cys Ser Pro Cys Ser  
                   50                  55                  60

105

Asn Phe Arg Ala Lys Thr Thr Pro Glu Cys Gly Pro Thr Gly Tyr Val  
 65 70 75 80

Glu Lys Ile Thr Cys Ser Ser Ser Lys Arg Asn Glu Phe Lys Ser Cys  
 85 90 95

Arg Phe Ser Phe Glu Trp Asn Asn Ala Tyr Phe Gly Ser Ser Lys Gly  
 100 105 110

Ala Val Val Cys Val Ala Leu Ile Phe Ala Cys Leu Val Ile Ile Arg  
 115 120 125

Gln Arg Gln Leu Asp Arg Lys Ala Leu Glu Lys Val Arg Lys Gln Ile  
 130 135 140

Glu Ser Ile Xaa  
 145

<210> 179  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (48)  
 <223> Xaa equals stop translation

<400> 179  
 Met Phe Met Cys Arg Leu Leu Leu Trp Ala Thr Gly Ala Tyr Gly Phe  
 1 5 10 15

Leu Gly Asp Asp Val Glu Tyr Thr Ser Val Leu Pro His Gln Lys Gly  
 20 25 30

Lys Glu Ala Trp Val Phe Ile Cys Gln Leu Pro Phe Ile Ile Gly Xaa  
 35 40 45

<210> 180  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE

106

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 180

Met Leu Gln Thr Leu Leu Cys Leu Trp Gln Tyr Thr Ser Ala Gln Val  
1 5 10 15

Leu Lys Met Leu Cys Ile His Arg Gln Lys Trp Asp Asn Phe Trp Ala  
20 25 30

Val Val Met Ile Asn Leu Leu Ile Arg Ile Gln Arg Leu Pro Phe Ser  
35 40 45

Leu Pro Ile Ala Leu Arg Val Xaa Xaa  
50 55

&lt;210&gt; 181

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 181

Met Pro Ser Glu Gly Arg Leu Val Leu Leu Ser Ala Phe Cys Pro Ala  
1 5 10 15

Phe Phe Pro Pro Trp Val Leu Ser Gly Ser Phe Ala Phe Ser Leu Cys  
20 25 30

Ala Glu Ser His Leu Asn Ser Ser His Arg Arg Ile Ala Val Trp Thr  
35 40 45

Xaa

&lt;210&gt; 182

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 182

Met Val Gln Trp Lys Asn Trp Pro Glu Ser Leu Glu Val Trp Val Leu  
1 5 10 15

Val	Leu	Ala	Val	Pro	Leu	Thr	His	Cys	Asp	Leu	Gly	Ile	Leu	Cys	Cys
			20					25					30		

Glu Asp Ile Ser Gln Val Leu His Val Ser Gln Gln Ile Xaa  
          35                    40                    45

```
<210> 183
<211> 41
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (41)
<223> Xaa equals stop translation
```

<400> 183  
Met Ala Leu Gly Leu Cys Ser Ser Gly Ala Leu Ser Thr Leu Cys Leu  
1 5 10 15

Ser Ser Val Thr Cys Leu Ala Ile Met Val Leu Met Ala Val Asp Gly  
20 25 30

Leu His Gly Thr Ser Gly Leu Gly Xaa  
35 40

```
<210> 184
<211> 80
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (80)
<223> Xaa equals stop translation
```

```
<400> 184
Met Thr Leu Met Cys Leu Cys Leu Ser Val Thr Val Leu His Pro Leu
  1             5             10             15
```

Arg Ser Lys Glu Arg Leu Ser Gly Thr Phe Cys Gly Tyr Ser Ser Ser  
20 25 30

Trp Cys Ser Pro Ala Ser Glu Ser Ser Ser Pro Gly Ser Leu Leu Thr  
35 40 45

Cys Ala Ala Ser Gly Ser His Pro Asp Cys Pro Leu Ser Gln Arg Leu  
50 55 60

Leu Gly Val Gln Leu Ala Ala Leu Gly Arg Pro Gln Gly Leu Phe Xaa  
65 70 75 80

<210> 185  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (47)  
 <223> Xaa equals stop translation

<400> 185  
 Met Lys Ser Gln Cys Tyr Ser Pro Ser Tyr Phe Ala Phe Phe Cys Leu  
           1                  5                  10                  15  
 Val Phe Phe Gln Ile Thr Ser Ala Ser Ser Gln Thr Leu Arg Gly His  
                   20                  25                  30  
 Val Leu Cys Arg Thr Thr Leu Arg Asp Ser Ser Ala Tyr Cys Xaa  
           35                  40                  45

<210> 186  
 <211> 141  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (36)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (141)  
 <223> Xaa equals stop translation

<400> 186  
 Met Phe Leu Phe Gly Gly Phe Leu Met Thr Leu Phe Gly Leu Phe Val  
           1                  5                  10                  15  
 Ser Leu Val Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val  
                   20                  25                  30  
 Trp Ser Arg Xaa Asn Pro Tyr Val Arg Met Asn Phe Phe Gly Leu Leu  
           35                  40                  45  
 Asn Phe Gln Ala Pro Phe Leu Pro Trp Val Leu Met Gly Phe Ser Leu  
           50                  55                  60  
 Leu Leu Gly Asn Ser Ile Ile Val Asp Leu Leu Gly Ile Ala Val Gly  
           65                  70                  75                  80



109

His Ile Tyr Phe Phe Leu Glu Asp Val Phe Pro Asn Gln Pro Gly Gly  
                     85                    90                    95

Ile Arg Ile Leu Lys Thr Pro Ser Ile Leu Lys Ala Ile Phe Asp Thr  
                     100                    105                    110

Pro Asp Glu Asp Pro Asn Tyr Asn Pro Leu Pro Glu Glu Arg Pro Gly  
                     115                    120                    125

Gly Phe Ala Trp Gly Glu Gly Gln Arg Leu Gly Gly Xaa  
                     130                    135                    140

<210> 187  
 <211> 339  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (339)  
 <223> Xaa equals stop translation

<400> 187  
 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu  
   1                    5                    10                    15

Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser  
                     20                    25                    30

Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Glu Arg Phe Phe Ala  
                     35                    40                    45

Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala  
                     50                    55                    60

Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu  
   65                    70                    75                    80

Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr  
                     85                    90                    95

Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser  
                     100                    105                    110

Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser  
                     115                    120                    125

Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Ala Ser Ala Glu Val  
                     130                    135                    140

Ser Pro Thr Thr Met Thr Ser Pro Ile Ser Pro His Phe Thr Val Thr  
   145                    150                    155                    160

Glu Arg Gln Thr Phe Gln Pro Trp Pro Glu Arg Leu Ser Asn Asn Val

110

	165		170		175
Glu Glu Leu Leu Gln Ser Ser Leu Ser Leu Gly Ser Gln Glu Gln Ala					
	180		185		190
Pro Glu His Lys Gln Glu Gln Gly Val Glu His Arg Gln Glu Pro Thr					
	195		200		205
Gln Glu His Lys Gln Glu Glu Gly Gln Lys Gln Glu Glu Gln Glu Glu					
	210		215		220
Glu Gln Glu Glu Glu Gly Lys Gln Glu Glu Gly Gln Gly Thr Lys Glu					
	225		230		235
Gly Arg Glu Ala Val Ser Gln Leu Gln Thr Asp Ser Glu Pro Lys Phe					
	245		250		255
His Ser Glu Ser Leu Ser Ser Asn Pro Ser Ser Phe Ala Pro Arg Val					
	260		265		270
Arg Glu Val Glu Ser Thr Pro Met Ile Met Glu Asn Ile Gln Glu Leu					
	275		280		285
Ile Arg Ser Ala Gln Glu Ile Asp Glu Met Asn Glu Ile Tyr Asp Glu					
	290		295		300
Asn Ser Tyr Trp Arg Asn Gln Asn Pro Gly Ser Leu Leu Gln Leu Pro					
	305		310		315
His Thr Glu Pro Cys Trp Cys Cys Ala Ile Arg Ser Trp Arg Ile Pro					
	325		330		335

Ala Ser Xaa

&lt;210&gt; 188

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (66)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 188

Met	Gln	Arg	Ile	Pro	Thr	Ser	Pro	Arg	Gln	Ala	Trp	Trp	Trp	Thr	Cys
1				5					10					15	

Trp	Ala	Met	Phe	Gln	Gly	Pro	Ala	Ala	Gly	Ser	Val	Gly	Ala	Glu	Arg
		20					25						30		

Lys	Gly	Glu	Gly	Cys	Leu	Phe	Phe	Gly	Gln	Asp	Glu	Ser	Ser	Arg	Cys
		35				40						45			

Gly Arg Ser Trp Pro Leu Ala Asp Pro Trp Val Tyr Arg Val Leu Arg  
 50 55 60

Ser Xaa  
 65

<210> 189  
 <211> 360  
 <212> PRT  
 <213> Homo sapiens

<400> 189  
 Met Val Pro Ala Ala Gly Arg Arg Pro Pro Arg Val Met Arg Leu Leu  
 1 5 10 15

Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu Pro Val Arg Gly  
 20 25 30

Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro  
 35 40 45

Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Glu Leu  
 50 55 60

Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu Glu Ala Asn Ala  
 65 70 75 80

Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val Met Leu Ser Val  
 85 90 95

Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu Pro Ser Gly Val  
 100 105 110

Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys Asn Val Arg Glu  
 115 120 125

Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe Pro Asp Arg Glu  
 130 135 140

Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser Asp Ala Ala Pro  
 145 150 155 160

Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser Pro Lys Val Asn  
 165 170 175

Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe Thr Leu Lys Ile  
 180 185 190

Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn Pro Asn Gly Ser  
 195 200 205

Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys Arg Phe Ser Ala  
 210 215 220

Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala Phe Pro Ala Leu  
 225 230 235 240  
 His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser Leu Ser Thr Arg  
 245 250 255  
 Phe Gly Thr Val Ala Val Pro Asn Ile Leu Leu Phe Gln Gly Ala Lys  
 260 265 270  
 Pro Met Ala Arg Phe Asn His Thr Asp Arg Thr Leu Glu Thr Leu Lys  
 275 280 285  
 Ile Phe Ile Phe Asn Gln Thr Gly Ile Glu Ala Lys Lys Asn Val Val  
 290 295 300  
 Val Thr Gln Ala Asp Gln Ile Gly Pro Leu Pro Ser Thr Leu Ile Lys  
 305 310 315 320  
 Ser Val Asp Trp Leu Leu Val Phe Ser Leu Phe Phe Leu Ile Ser Phe  
 325 330 335  
 Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg Trp Leu Ile Pro  
 340 345 350  
 Gly Gln Glu Gln Glu His Val Glu  
 355 360

<210> 190  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (160)  
 <223> Xaa equals stop translation

<400> 190  
 Met Leu Leu Leu Leu Ile Phe Trp Ile Ala Pro Ala His Gly Pro Thr  
 1 5 10 15  
 Asn Ile Met Val Tyr Ile Ser Ile Cys Ser Leu Leu Gly Ser Phe Thr  
 20 25 30  
 Val Pro Ser Thr Lys Gly Ile Gly Leu Ala Ala Gln Asp Ile Leu His  
 35 40 45  
 Asn Asn Pro Ser Ser Gln Arg Ala Leu Cys Leu Cys Leu Val Leu Leu  
 50 55 60  
 Ala Val Leu Gly Cys Ser Ile Ile Val Gln Phe Arg Tyr Ile Asn Lys  
 65 70 75 80

113

Ala Leu Glu Cys Phe Asp Ser Ser Val Phe Gly Ala Ile Tyr Tyr Val  
                     85                    90                    95

Val Phe Thr Thr Leu Val Leu Leu Ala Ser Ala Ile Leu Phe Arg Glu  
                     100                    105                    110

Trp Ser Asn Val Gly Leu Val Asp Phe Leu Gly Met Ala Cys Gly Phe  
                     115                    120                    125

Thr Thr Val Ser Val Gly Ile Val Leu Ile Gln Val Phe Lys Glu Phe  
                     130                    135                    140

Asn Phe Asn Leu Gly Glu Met Asn Lys Ser Asn Met Lys Thr Asp Xaa  
                     145                    150                    155                    160

&lt;210&gt; 191

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (92)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (96)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (101)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 191

Met Phe Val Ala Val Phe Tyr Trp Val Leu Thr Val Phe Phe Leu Ile  
   1                    5                    10                    15

Ile Tyr Ile Thr Met Thr Tyr Thr Arg Ile Pro Gln Val Pro Trp Thr  
                     20                    25                    30

Thr Val Gly Leu Cys Phe Asn Gly Ser Ala Phe Val Leu Tyr Leu Ser  
                     35                    40                    45

Ala Ala Val Val Asp Ala Ser Ser Val Ser Pro Glu Lys Asp Ser His  
                     50                    55                    60

Asn Phe Asn Ser Trp Ala Ala Ser Ser Phe Phe Ala Phe Leu Val Thr  
   65                    70                    75                    80

114

Ile Cys Tyr Ala Gly Asn Thr Tyr Phe Ser Phe Xaa Ala Trp Arg Xaa  
                     85                    90                    95

Arg Thr Ile Gln Xaa  
                     100

<210> 192  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 192  
 Met Phe Lys Leu Gln Leu Asp Leu Leu Thr Ala Val Asn Leu Val Tyr  
     1                    5                    10                    15

Phe Ser Phe Leu Trp Val Val Ser Val Ala Asn Lys Met Asp Val Ser  
                     20                    25                    30

Val Phe Glu Leu Val Asn Ser Asp Cys Phe Xaa  
                     35                    40

<210> 193  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals stop translation

<400> 193  
 Met Ser Val Cys Val Phe Leu Asp Phe Arg Leu Ile Phe Trp Ser Phe  
     1                    5                    10                    15

Cys Pro Cys Ser Ala Ser Pro Ser Arg His Phe Ala Ser Ser Ser Arg  
                     20                    25                    30

Gly Gly Gly Gly Gly Ser Arg Asn Trp Val Gly Ala Gly Ala Ser Leu  
                     35                    40                    45

Ala Ala Ser Leu Ala Leu Tyr Ala Leu Ser Pro Arg Arg Xaa  
                     50                    55                    60

<210> 194  
 <211> 53  
 <212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (53)

<223> Xaa equals stop translation

<400> 194

Met Gln Ala Gln Ile Ser Ser Pro Arg Trp Thr Ser Trp Phe Ser Leu  
1 5 10 15

Thr Ala Val Thr Leu Ala Phe Pro Ser Leu Ile Pro Tyr Pro Ser Cys  
20 25 30

Gly Ile Pro Val Leu Thr Gln Asp Ala Lys Trp Pro Ser Asp Tyr Thr  
35 40 45

Ser Pro Asp Ser Xaa  
50

<210> 195

<211> 186

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (114)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (186)

<223> Xaa equals stop translation

<400> 195

Met Thr Leu Leu Asn Leu Leu Leu Gln Thr Ile Phe Tyr Gly Val Thr  
1 5 10 15

Cys Leu Asp Asp Val Leu Lys Arg Thr Lys Gly Gly Lys Asp Ile Lys  
20 25 30

Phe Leu Thr Ala Phe Arg Asp Leu Leu Phe Thr Thr Leu Ala Phe Pro  
35 40 45

Val Ser Thr Phe Val Phe Leu Ala Phe Trp Ile Leu Phe Leu Tyr Asn  
50 55 60

Arg Asp Leu Ile Tyr Pro Lys Val Leu Asp Thr Val Ile Pro Val Trp  
65 70 75 80

Leu Asn His Ala Met His Thr Phe Ile Phe Pro Ile Thr Leu Ala Glu  
85 90 95

116

Val Val Leu Arg Pro His Ser Tyr Pro Ser Lys Lys Thr Gly Leu Thr  
                   100                  105                  110  
 Leu Xaa Ala Ala Ala Ser Ile Ala Tyr Ile Ser Arg Ile Leu Trp Leu  
                   115                  120                  125  
 Tyr Phe Glu Thr Gly Thr Trp Val Tyr Pro Val Phe Ala Lys Leu Ser  
           130                  135                  140  
 Leu Leu Gly Leu Ala Ala Phe Phe Ser Leu Ser Tyr Val Phe Ile Ala  
 145                  150                  155                  160  
 Ser Ile Tyr Leu Leu Gly Glu Lys Leu Asn His Trp Lys Trp Gly Asp  
                   165                  170                  175  
 Met Arg Gln Pro Arg Lys Lys Arg Lys Xaa  
                   180                  185

<210> 196  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (77)  
 <223> Xaa equals stop translation

<400> 196  
 Met Lys Asn Ala Thr Leu Leu Arg Met Val Leu Phe Val Ile Asn Leu  
   1                  5                  10                  15  
 Gln Asn Leu Lys Ser Cys Pro Val Leu His Ile His Gln Asp Val Gln  
                   20                  25                  30  
 Gln Gln Lys Arg Met Gly His Gly Gly Ser Ser Thr Arg Val Thr Val  
           35                  40                  45  
 Thr Ser Leu Ile Arg His Cys Thr Val Phe Gln Arg Pro Lys Asn Cys  
   50                  55                  60  
 Val Gln Asn Met Ile Thr Leu Gln Leu Ser Phe Pro Xaa  
   65                  70                  75

<210> 197  
 <211> 175  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (175)  
 <223> Xaa equals stop translation



117

&lt;400&gt; 197

```

Met Phe Val Pro Ser Cys Leu Cys Leu Arg Phe Val Val Thr Ser Leu
 1             5             10             15

Leu Leu Gln Met Thr His Ser Cys Gly Gly Phe Tyr Ile Cys Val Ile
          20             25             30

Phe Glu Thr Ile Leu Ser Glu Phe Lys Thr Gln Ile Gly Arg Leu Tyr
          35             40             45

Arg Lys Arg Arg His Ile Gln Arg Lys Glu Ser Pro Lys Gly Arg Phe Val
          50             55             60

Met Leu Leu Pro Ser Ser Thr His Thr Ile Pro Phe Tyr Pro Asn Pro
          65             70             75             80

Leu His Pro Arg Pro Phe Pro Ser Ser Arg Leu Pro Pro Gly Ile Ile
          85             90             95

Gly Gly Glu Tyr Asp Gln Arg Pro Thr Leu Pro Tyr Val Gly Asp Pro
          100             105             110

Ile Ser Ser Leu Ile Pro Gly Pro Gly Glu Thr Pro Ser Gln Phe Pro
          115             120             125

Pro Leu Arg Pro Arg Phe Asp Pro Val Gly Pro Leu Pro Gly Pro Asn
          130             135             140

Pro Ile Leu Pro Gly Arg Gly Gly Pro Asn Asp Arg Phe Pro Phe Arg
          145             150             155             160

Pro Ser Arg Gly Arg Pro Thr Asp Gly Arg Leu Ser Phe Met Xaa
          165             170             175

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&lt;210&gt; 198

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 198

```

Met Gly Leu Lys Arg Lys Gln Gly Phe Val Phe Leu Phe Leu Leu Leu
 1             5             10             15

Lys Ser Thr Val Ala Ser Trp Leu Leu Ser Gly Val Gly Arg Ile Trp
          20             25             30

Gly Leu Val His Phe Val Lys Val Asn His Val Cys Leu Asn Asn Arg
          35             40             45

```

Gly Val Xaa  
50

<210> 199

<211> 190

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (190)

<223> Xaa equals stop translation

<400> 199

Met Gly Pro Val Arg Leu Gly Ile Leu Leu Phe Leu Phe Leu Ala Val  
1 5 10 15

His Glu Ala Trp Ala Gly Met Leu Lys Glu Glu Asp Asp Asp Thr Glu  
20 25 30

Arg Leu Pro Ser Lys Cys Glu Val Cys Lys Leu Leu Ser Thr Glu Leu  
35 40 45

Gln Ala Glu Leu Ser Arg Thr Gly Arg Ser Arg Glu Val Leu Glu Leu  
50 55 60

Gly Gln Val Leu Asp Thr Gly Lys Arg Lys Arg His Val Pro Tyr Ser  
65 70 75 80

Val Ser Glu Thr Arg Leu Glu Glu Ala Leu Glu Asn Leu Cys Glu Arg  
85 90 95

Ile Leu Asp Tyr Ser Val His Ala Glu Arg Lys Gly Ser Leu Arg Tyr  
100 105 110

Ala Lys Gly Gln Ser Gln Thr Met Ala Thr Leu Lys Gly Leu Val Gln  
115 120 125

Lys Gly Val Lys Val Asp Leu Gly Ile Pro Leu Glu Leu Trp Asp Glu  
130 135 140

Pro Ser Val Glu Val Thr Tyr Leu Lys Lys Gln Cys Glu Thr Met Leu  
145 150 155 160

Glu Glu Glu Glu Glu Glu Glu Glu Glu Gly Gly Asp Lys Met Thr  
165 170 175

Lys Thr Gly Ser His Pro Lys Leu Asp Arg Glu Asp Leu Xaa  
180 185 190

<210> 200

<211> 80

119

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 200

```

Met Asn Tyr Ser Arg Ser Pro Trp Ala Ala Val Met Glu Pro Leu Thr
  1              5              10              15
Leu Leu Phe Leu His Leu Ser Cys Leu Leu Ser Leu Cys Glu Ala Val
              20              25              30
Gly Trp Asp Ser Glu Cys Leu Val Cys Ser Leu Gly Glu Glu Glu Phe
              35              40              45
Leu Arg Met Gln Ala Leu Leu Cys Gly Cys Arg Leu His Leu Gly Gly
              50              55              60
Val Leu Tyr Val Cys Thr Leu Gly Thr Ala Cys Ile Trp Lys Ile Xaa
  65              70              75              80

```

&lt;210&gt; 201

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (106)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 201

```

Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val
  1              5              10              15
Gly Gly Ala Gln Val Leu Ala Thr Gly Lys Thr Pro Gly Ala Glu Ile
              20              25              30
Asp Phe Lys Tyr Ala Leu Ile Gly Thr Ala Val Gly Val Ala Ile Ser
              35              40              45
Ala Gly Phe Leu Ala Leu Lys Ile Cys Met Ile Arg Arg His Leu Phe
              50              55              60
Asp Asp Asp Ser Ser Asp Leu Lys Ser Thr Pro Gly Gly Leu Ser Asp
  65              70              75              80
Thr Ile Pro Leu Lys Lys Arg Ala Pro Arg Arg Asn His Asn Phe Ser

```

120

85 90 95  
 Lys Arg Asp Ala Gln Val Ile Glu Leu Xaa  
 100 105  
  
 <210> 202  
 <211> 80  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (80)  
 <223> Xaa equals stop translation  
  
 <400> 202  
 Met Ala Cys Leu Gly Gly Leu Leu Gly Ile Ile Gly Val Ile Cys Leu  
 1 5 10 15  
 Ile Ser Cys Leu Ser Pro Glu Met Asn Cys Asp Gly Gly His Ser Tyr  
 20 25 30  
 Val Arg Asn Tyr Leu Gln Lys Pro Thr Phe Ala Leu Gly Glu Leu Tyr  
 35 40 45  
 Pro Pro Leu Ile Asn Leu Trp Glu Ala Gly Lys Glu Lys Ser Thr Ser  
 50 55 60  
 Leu Lys Val Lys Ala Thr Val Ile Gly Leu Pro Thr Asn Met Ser Xaa  
 65 70 75 80

<210> 203  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals stop translation  
  
 <400> 203  
 Met Gly Leu Lys Leu Leu Gln Lys Pro Gly Ser Leu Lys Thr Leu Ile  
 1 5 10 15  
 Ala Ile Ile Leu Val Met Tyr Ile Phe Met Thr Ile Ser Val Ile Ala  
 20 25 30  
 Gly Thr Gly Lys Phe Ser Gln Lys Leu Asp Leu His Leu Asn Met Asp  
 35 40 45

Ile Ser Pro Gly Arg Pro Ser Val His Xaa  
 50 55

<210> 204

<211> 161

<212> PRT

<213> Homo sapiens

<400> 204

Met Asp Phe Leu Asn Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe  
 1 5 10 15

Tyr Thr Pro Trp Cys Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn  
 20 25 30

Ser Leu Pro Arg Ala Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala  
 35 40 45

Ser Gln His Ser Ser Leu Ser Thr Arg Phe Gly Thr Val Ala Val Pro  
 50 55 60

Asn Ile Leu Leu Phe Gln Gly Ala Lys Pro Met Ala Arg Phe Asn His  
 65 70 75 80

Thr Asp Arg Thr Leu Glu Thr Leu Lys Ile Phe Ile Phe Asn Gln Thr  
 85 90 95

Gly Ile Glu Ala Lys Lys Asn Val Val Val Thr Gln Ala Asp Gln Ile  
 100 105 110

Gly Pro Leu Pro Ser Thr Leu Ile Lys Ser Val Asp Trp Leu Leu Val  
 115 120 125

Phe Ser Leu Phe Phe Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg  
 130 135 140

Thr Glu Ser Ile Arg Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val  
 145 150 155 160

Glu

<210> 205

<211> 137

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

122

&lt;400&gt; 205

Ile Pro Glu Asn Arg Arg Pro Ala Ser Xaa Cys Thr Trp Ser Met Trp  
 1 5 10 15

Thr Ser Arg Thr Thr Thr Arg Arg Pro Pro Trp Gly Arg Phe Ser Ser  
 20 25 30

Val Ser Ser Ala Ser Val Ser Ser Thr Arg Lys Thr Trp Arg Thr Arg  
 35 40 45

Ser Thr Ser Cys Cys Arg Ser Ser Arg Arg Arg Val Ala Ala Pro Phe  
 50 55 60

Cys Thr Pro Ser Ala Ser Thr Glu Pro Ser Ala Arg Met Glu Pro Pro  
 65 70 75 80

Leu Glu Leu Pro Val Val His Thr Phe Ser Phe Leu Thr Phe Val Phe  
 85 90 95

Thr Tyr Arg Cys Ser Ala Gly Asp Gly Ser Ile Thr Gln Ile Asn Cys  
 100 105 110

Ala Tyr Glu Met Gly Glu Glu Met Pro Lys Arg Gln Met Lys Ala Ile  
 115 120 125

Lys Phe Leu Leu Phe His Phe Tyr Leu  
 130 135

&lt;210&gt; 206

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 206

Ile Pro Glu Asn Arg Arg Pro Ala Ser Xaa Cys Thr Trp Ser Met Trp  
 1 5 10 15

Thr Ser Arg Thr Thr Thr Arg Arg Pro Pro Trp Gly Arg Phe Ser Ser  
 20 25 30

Val Ser Ser Ala Ser Val Ser Ser Thr  
 35 40

&lt;210&gt; 207

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

123

&lt;400&gt; 207

Arg Lys Thr Trp Arg Thr Arg Ser Thr Ser Cys Cys Arg Ser Ser Arg  
 1 5 10 15

Arg Arg Val Ala Ala Pro Phe Cys Thr Pro Ser Ala Ser Thr Glu Pro  
 20 25 30

Ser Ala Arg Met Glu Pro Pro Leu Glu Leu Pro  
 35 40

&lt;210&gt; 208

&lt;211&gt; 53

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 208

Val Val His Thr Phe Ser Phe Leu Thr Phe Val Phe Thr Tyr Arg Cys  
 1 5 10 15

Ser Ala Gly Asp Gly Ser Ile Thr Gln Ile Asn Cys Ala Tyr Glu Met  
 20 25 30

Gly Glu Glu Met Pro Lys Arg Gln Met Lys Ala Ile Lys Phe Leu Leu  
 35 40 45

Phe His Phe Tyr Leu  
 50

&lt;210&gt; 209

&lt;211&gt; 223

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 209

His Pro Ser Ile Ile Ile Trp Ser Gly Asn Asn Glu Asn Glu Glu Ala  
 1 5 10 15

Leu Met Met Asn Trp Tyr His Ile Ser Phe Thr Asp Arg Pro Ile Tyr  
 20 25 30

Ile Lys Asp Tyr Val Thr Leu Tyr Val Lys Asn Ile Arg Glu Leu Val  
 35 40 45

Leu Ala Gly Asp Lys Ser Arg Pro Phe Ile Thr Ser Ser Pro Thr Asn  
 50 55 60

Gly Ala Glu Thr Val Ala Glu Ala Trp Val Ser Gln Asn Pro Asn Ser  
 65 70 75 80

Asn Tyr Phe Gly Asp Val His Phe Tyr Asp Tyr Ile Ser Asp Cys Trp  
 85 90 95

Asn Trp Lys Val Phe Pro Lys Ala Arg Phe Ala Ser Glu Tyr Gly Tyr

124

100					105					110						
Gln	Ser	Trp	Pro	Ser	Phe	Ser	Thr	Leu	Glu	Lys	Val	Ser	Ser	Thr	Glu	
115					120					125						
Asp	Trp	Ser	Phe	Asn	Ser	Lys	Phe	Ser	Leu	His	Arg	Gln	His	His	Glu	
130					135					140						
Gly	Gly	Asn	Lys	Gln	Met	Leu	Tyr	Gln	Ala	Gly	Leu	His	Phe	Lys	Leu	
145					150					155					160	
Pro	Gln	Ser	Thr	Asp	Pro	Leu	Arg	Thr	Phe	Lys	Asp	Thr	Ile	Tyr	Leu	
165					170					175						
Thr	Gln	Val	Met	Gln	Ala	Gln	Cys	Val	Lys	Thr	Glu	Thr	Glu	Phe	Tyr	
180					185					190						
Arg	Arg	Ser	Arg	Ser	Glu	Ile	Val	Asp	Gln	Gln	Gly	His	Thr	Met	Gly	
195					200					205						
Ala	Leu	Tyr	Trp	Gln	Leu	Asn	Asp	Ile	Trp	Gln	Ala	Pro	Ser	Trp		
210					215					220						
<210> 210																
<211> 160																
<212> PRT																
<213> Homo sapiens																
<400> 210																
Val	Arg	Val	His	Thr	Trp	Ser	Ser	Leu	Glu	Pro	Val	Cys	Ser	Arg	Val	
1				5					10					15		
Thr	Glu	Arg	Phe	Val	Met	Lys	Gly	Gly	Glu	Ala	Val	Cys	Leu	Tyr	Glu	
20					25					30						
Glu	Pro	Val	Ser	Glu	Leu	Leu	Arg	Arg	Cys	Gly	Asn	Cys	Thr	Arg	Glu	
35					40					45						
Ser	Cys	Val	Val	Ser	Phe	Tyr	Leu	Ser	Ala	Asp	His	Glu	Leu	Leu	Ser	
50					55					60						
Pro	Thr	Asn	Tyr	His	Phe	Leu	Ser	Ser	Pro	Lys	Glu	Ala	Val	Gly	Leu	
65					70					75					80	
Cys	Lys	Ala	Gln	Ile	Thr	Ala	Ile	Ile	Ser	Gln	Gln	Gly	Asp	Ile	Phe	
85					90					95						
Val	Phe	Asp	Leu	Glu	Thr	Ser	Ala	Val	Ala	Pro	Phe	Val	Trp	Leu	Asp	
100					105					110						
Val	Gly	Ser	Ile	Pro	Gly	Arg	Phe	Ser	Asp	Asn	Gly	Phe	Leu	Met	Thr	
115					120					125						
Glu Lys Thr Arg Thr Ile Leu Phe Tyr Pro Trp Glu Pro Thr Ser Lys																



125

130

135

140

Asn Glu Leu Glu Gln Ser Phe His Val Thr Ser Leu Thr Asp Ile Tyr  
 145 150 155 160

&lt;210&gt; 211

&lt;211&gt; 171

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (102)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 211

Pro Arg Leu Thr Pro Arg Met Lys Trp Pro Thr Ala Ala Leu Ala Ser  
 1 5 10 15

Arg Leu Leu Gly Trp Thr Val Leu Arg Pro Pro Tyr Pro Arg Val Pro  
 20 25 30

Ser Leu Pro Gln Val Thr Leu His Pro Thr Asp Gly Leu Met Ala Val  
 35 40 45

Leu Tyr Thr Gly Gly Glu Gly Arg Thr Leu Gly Glu Gln His Phe Phe  
 50 55 60

His Glu Thr Phe Val Thr Arg Trp Leu Leu Gly Pro Val Pro Val Arg  
 65 70 75 80

Phe Gly Ala Cys Ser Pro Leu Ser Phe Leu Ala Pro Arg Arg Gly Gln  
 85 90 95

Gly Ala Pro Ala Gly Xaa Phe Cys Ala Cys Pro Arg Pro Ala Ser Arg  
 100 105 110

Gln Leu Cys Pro Trp Pro Ala Leu Pro Gly Thr Pro Tyr Ser Asn Ser  
 115 120 125

Ala Pro Leu Cys Thr Gly Met Gly His Ser Asn Thr Pro Gln Gly Pro  
 130 135 140

Pro Ser Pro Gln Tyr Ala Leu Ser Pro Thr Glu Pro Thr Ser Leu Ser  
 145 150 155 160

Gly Asn Ser His Leu Pro Ala Ile Leu Val Leu  
 165 170

&lt;210&gt; 212

126

<211> 41  
<212> PRT  
<213> Homo sapiens

<400> 212  
Pro Arg Leu Thr Pro Arg Met Lys Trp Pro Thr Ala Ala Leu Ala Ser  
1 5 10 15  
Arg Leu Leu Gly Trp Thr Val Leu Arg Pro Pro Tyr Pro Arg Val Pro  
20 25 30  
Ser Leu Pro Gln Val Thr Leu His Pro  
35 40

<210> 213  
<211> 41  
<212> PRT  
<213> Homo sapiens

<400> 213  
Thr Asp Gly Leu Met Ala Val Leu Tyr Thr Gly Gly Glu Gly Arg Thr  
1 5 10 15  
Leu Gly Glu Gln His Phe Phe His Glu Thr Phe Val Thr Arg Trp Leu  
20 25 30  
Leu Gly Pro Val Pro Val Arg Phe Gly  
35 40

<210> 214  
<211> 42  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (20)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 214  
Ala Cys Ser Pro Leu Ser Phe Leu Ala Pro Arg Arg Gly Gln Gly Ala  
1 5 10 15  
Pro Ala Gly Xaa Phe Cys Ala Cys Pro Arg Pro Ala Ser Arg Gln Leu  
20 25 30  
Cys Pro Trp Pro Ala Leu Pro Gly Thr Pro  
35 40

<210> 215  
<211> 47  
<212> PRT

<213> Homo sapiens

<400> 215

Tyr Ser Asn Ser Ala Pro Leu Cys Thr Gly Met Gly His Ser Asn Thr  
 1 5 10 15  
 Pro Gln Gly Pro Pro Ser Pro Gln Tyr Ala Leu Ser Pro Thr Glu Pro  
 20 25 30  
 Thr Ser Leu Ser Gly Asn Ser His Leu Pro Ala Ile Leu Val Leu  
 35 40 45

<210> 216

<211> 27

<212> PRT

<213> Homo sapiens

<400> 216

His Leu Leu Glu Val Thr Pro Cys Arg Leu Pro Val Pro Glu Phe Pro  
 1 5 10 15  
 Gly Arg Thr Pro Arg Gly Ser Arg Thr Pro Asp  
 20 25

<210> 217

<211> 239

<212> PRT

<213> Homo sapiens

<400> 217

Met Ile Pro Gly Ser Asp Ser Gln Thr Ala Leu Asn Phe Gly Ser Thr  
 1 5 10 15  
 Leu Met Lys Lys Lys Ser Asp Pro Glu Gly Pro Ala Leu Leu Phe Pro  
 20 25 30  
 Glu Ser Glu Leu Ser Ile Arg Ile Gly Arg Ala Gly Leu Leu Ser Asp  
 35 40 45  
 Lys Ser Glu Asn Gly Glu Ala Tyr Gln Arg Lys Lys Ala Ala Ala Thr  
 50 55 60  
 Gly Leu Pro Glu Gly Pro Ala Val Pro Val Pro Ser Arg Gly Asn Leu  
 65 70 75 80  
 Ala Gln Pro Gly Gly Ser Ser Trp Arg Arg Ile Ala Leu Leu Ile Leu  
 85 90 95  
 Ala Ile Thr Ile His Asn Val Pro Glu Gly Leu Ala Val Gly Val Gly  
 100 105 110  
 Phe Gly Ala Ile Glu Lys Thr Ala Ser Ala Thr Phe Glu Ser Ala Arg  
 115 120 125

Asn Leu Ala Ile Gly Ile Gly Ile Gln Asn Phe Pro Glu Gly Leu Ala  
 130 135 140

Val Ser Leu Pro Leu Arg Gly Ala Gly Phe Ser Thr Trp Arg Ala Phe  
 145 150 155 160

Trp Tyr Gly Gln Leu Ser Gly Met Val Glu Pro Leu Ala Gly Val Phe  
 165 170 175

Gly Ala Phe Ala Val Val Leu Ala Glu Pro Ile Leu Pro Tyr Ala Leu  
 180 185 190

Ala Phe Ala Ala Gly Ala Met Val Tyr Val Val Met Asp Asp Ile Ile  
 195 200 205

Pro Glu Ala Gln Ile Ser Gly Asn Gly Lys Leu Ala Ser Trp Ala Ser  
 210 215 220

Ile Leu Gly Phe Val Val Met Met Ser Leu Asp Val Gly Leu Gly  
 225 230 235

<210> 218

<211> 43

<212> PRT

<213> Homo sapiens

<400> 218

Met Ile Pro Gly Ser Asp Ser Gln Thr Ala Leu Asn Phe Gly Ser Thr  
 1 5 10 15

Leu Met Lys Lys Lys Ser Asp Pro Glu Gly Pro Ala Leu Leu Phe Pro  
 20 25 30

Glu Ser Glu Leu Ser Ile Arg Ile Gly Arg Ala  
 35 40

<210> 219

<211> 41

<212> PRT

<213> Homo sapiens

<400> 219

Gly Leu Leu Ser Asp Lys Ser Glu Asn Gly Glu Ala Tyr Gln Arg Lys  
 1 5 10 15

Lys Ala Ala Ala Thr Gly Leu Pro Glu Gly Pro Ala Val Pro Val Pro  
 20 25 30

Ser Arg Gly Asn Leu Ala Gln Pro Gly  
 35 40

129

&lt;210&gt; 220

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 220

Gly Ser Ser Trp Arg Arg Ile Ala Leu Leu Ile Leu Ala Ile Thr Ile  
 1 5 10 15

His Asn Val Pro Glu Gly Leu Ala Val Gly Val Gly Phe Gly Ala Ile  
 20 25 30

Glu Lys Thr Ala Ser Ala Thr Phe Glu Ser Ala Arg  
 35 40

&lt;210&gt; 221

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 221

Asn Leu Ala Ile Gly Ile Gly Ile Gln Asn Phe Pro Glu Gly Leu Ala  
 1 5 10 15

Val Ser Leu Pro Leu Arg Gly Ala Gly Phe Ser Thr Trp Arg Ala Phe  
 20 25 30

Trp Tyr Gly Gln Leu Ser Gly Met Val Glu Pro  
 35 40

&lt;210&gt; 222

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 222

Leu Ala Gly Val Phe Gly Ala Phe Ala Val Val Leu Ala Glu Pro Ile  
 1 5 10 15

Leu Pro Tyr Ala Leu Ala Phe Ala Ala Gly Ala Met Val Tyr Val Val  
 20 25 30

Met Asp Asp Ile Ile Pro Glu Ala Gln Ile Ser  
 35 40

&lt;210&gt; 223

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 223

Gly Asn Gly Lys Leu Ala Ser Trp Ala Ser Ile Leu Gly Phe Val Val

130

**1                      5                      10                      15**

Met Met Ser Leu Asp Val Gly Leu Gly  
20 25

<210> 224

<211> 11

<212> PRT

<213> Homo sapiens

<400> 224

Thr Arg Pro Ile Thr Tyr Val Leu Leu Ala Gly  
1 5 10

<210> 225

<211> 35

<212> PRT

<213> Homo sapiens

<400> 225

Gly Thr Ser Leu Thr Ala Pro Leu Leu Glu Phe Leu Leu Ala Leu Tyr  
1 5 10 15

Phe Leu Phe Ala Asp Ala Met Gln Leu Asn Asp Lys Trp Gln Gly Leu  
20 25 30

Cys Trp Pro  
35

<210> 226

<211> 30

<212> PRT

<213> Homo sapiens

<400> 226

Leu Ala Asn Phe Glx Cys Ser Asp Cys Ala Gln Thr Val Leu Phe Val  
1 5 10 15

Leu Glx Phe Glx Ile Leu Val Phe Thr Tyr Glu Ile Pro Phe  
20 25 30

<210> 227

<211> 75

<212> PRT

<213> Homo sapiens

<400> 227

Gln Ala Trp His Glu Val Gly Gly Gly Val Arg Arg Cys Trp Phe Val  
1 5 10 15

Leu Gly Glu Arg Arg Ala Gly Ser Leu Leu Ser Ala Ser Tyr Gly Thr

131

20	25	30
Phe Ala Met Pro Gly Met Val Leu Phe Gly Arg Arg Trp Ala Ile Ala		
35	40	45
Ser Asp Asp Leu Val Phe Pro Gly Phe Phe Glu Leu Val Val Arg Val		
50	55	60
Leu Trp Trp Ile Gly Ile Leu Thr Leu Tyr Leu		
65	70	75

<210> 228  
 <211> 125  
 <212> PRT  
 <213> Homo sapiens

<400> 228
Pro Gly Met Val Leu Phe Gly Arg Arg Trp Ala Ile Ala Ser Asp Asp
1 5 10 15
Leu Val Phe Pro Gly Phe Phe Glu Leu Val Val Arg Val Leu Trp Trp
20 25 30
Ile Gly Ile Leu Thr Leu Tyr Leu Met His Arg Gly Lys Leu Asp Cys
35 40 45
Ala Gly Gly Ala Leu Leu Ser Ser Tyr Leu Ile Val Leu Met Ile Leu
50 55 60
Leu Ala Val Val Ile Cys Thr Val Ser Ala Ile Met Cys Val Ser Met
65 70 75 80
Arg Gly Thr Ile Cys Asn Pro Gly Pro Arg Lys Ser Met Ser Lys Leu
85 90 95
Leu Tyr Ile Arg Leu Ala Leu Phe Phe Pro Glu Met Val Trp Ala Ser
100 105 110
Leu Gly Ala Ala Trp Val Ala Asp Gly Val Gln Cys Asp
115 120 125

<210> 229  
 <211> 18  
 <212> PRT  
 <213> Homo sapiens

<400> 229
His Glu Arg Asn Cys Phe Pro Met Trp Leu Asn His Ser Ala Phe Pro
1 5 10 15
Pro Val

132

&lt;210&gt; 230

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 230

Gly Trp Thr Arg Glu Asn Asp His Arg Ala Leu Ser Lys Ala Gly Ile  
 1 5 10 15

Gly Ser Ala Glu Ile Gln Pro Ser Asn Leu Arg Val Gly Ser Ala Lys  
 20 25 30

Asp Leu Gly Lys Pro Trp Ala Gly Lys Leu Leu Leu Leu Ser Ser Cys  
 35 40 45

Leu Leu Phe Phe Ser Leu Gly Val Leu Tyr Arg Gly Gln Met Leu Ala  
 50 55 60

Pro Pro Leu Gln Glu Asp Trp Lys Gly Gly Val Lys Asp Ser Asp Leu  
 65 70 75 80

Ile Asp Asp Ser Ser Ala Ser Pro Ile Pro Pro Ser Tyr Leu Glu Tyr  
 85 90 95

Lys Ala Ala Leu Tyr Pro Phe Ser Glu His Lys Ser Val Arg Asn Ala  
 100 105 110

Thr Asp Ser Leu Thr Phe Phe Leu Val Thr Asp His Phe Leu Asp Asn  
 115 120 125

Gln Asp Ser Gln  
 130

&lt;210&gt; 231

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 231

Gly Trp Thr Arg Glu Asn Asp His Arg Ala Leu Ser Lys Ala Gly Ile  
 1 5 10 15

Gly Ser Ala Glu Ile Gln Pro Ser Asn Leu Arg Val Gly Ser Ala Lys  
 20 25 30

Asp Leu Gly Lys Pro Trp Ala Gly Lys Leu Leu Leu Leu  
 35 40 45

&lt;210&gt; 232

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens



&lt;400&gt; 232

Ser Ser Cys Leu Leu Phe Phe Ser Leu Gly Val Leu Tyr Arg Gly Gln  
 1 5 10 15

Met Leu Ala Pro Pro Leu Gln Glu Asp Trp Lys Gly Gly Val Lys Asp  
 20 25 30

Ser Asp Leu Ile Asp Asp Ser Ser Ala Ser Pro Ile Pro Pro  
 35 40 45

&lt;210&gt; 233

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 233

Ser Tyr Leu Glu Tyr Lys Ala Ala Leu Tyr Pro Phe Ser Glu His Lys  
 1 5 10 15

Ser Val Arg Asn Ala Thr Asp Ser Leu Thr Phe Phe Leu Val Thr Asp  
 20 25 30

His Phe Leu Asp Asn Gln Asp Ser Gln  
 35 40

&lt;210&gt; 234

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 234

Leu Lys Phe His Gln Glu Ser Leu Ser Gly Asp  
 1 5 10

&lt;210&gt; 235

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 235

Glu Ala Lys Ser Arg Pro Val Thr Gln Ala Gly Val Gln Trp His Asp  
 1 5 10 15

Leu Gly Ser Leu Gln Pro Leu Pro Pro  
 20 25

&lt;210&gt; 236

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 236

Glu Ala Lys Ser Arg Pro Val Thr Gln Ala Gly Val Gln Trp His Asp  
 1 5 10 15

Leu Gly Ser Leu Gln Pro Leu Pro Pro  
 20 25

&lt;210&gt; 237

&lt;211&gt; 137

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 237

Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys Arg Pro Arg Asp Leu  
 1 5 10 15

Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp Leu Ile Gly Ala Met  
 20 25 30

Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu Asp Asp Val Val Ile  
 35 40 45

Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn Glu Asp Trp Ile Glu  
 50 55 60

Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala Ile Leu Lys Ile Cys  
 65 70 75 80

His Thr Leu Thr Glu Lys Leu Val Ala Met Thr Met Gly Ser Gly Ala  
 85 90 95

Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile Ile Val Val Ala Lys  
 100 105 110

Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys Ser Met Tyr Pro Pro  
 115 120 125

Leu Asp Pro Lys Leu Leu Asp Ala Arg  
 130 135

&lt;210&gt; 238

&lt;211&gt; 319

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 238

Asp Val Glu Ser Arg Gly Pro Ser Ala Arg Cys Leu Pro Val Val Pro  
 1 5 10 15

Gly Ser Leu Leu Pro Gly Leu Glu Pro Ala Thr Lys Leu Met Pro Gly  
 20 25 30

Gly Leu Ala Pro Gly His Gly Ala Pro Val Arg Glu Leu Leu Leu Pro  
           35                                  40                                  45

Leu Leu Ser Gln Pro Thr Leu Gly Ser Leu Trp Asp Ser Leu Arg His  
           50                                  55                                  60

Cys Ser Leu Leu Cys Asn Pro Leu Ser Cys Val Pro Ala Leu Glu Ala  
           65                                  70                                  75                                  80

Pro Pro Ser Leu Val Ser Leu Gly Cys Ser Gly Gly Cys Pro Arg Leu  
                                   85                                  90                                  95

Ser Leu Ala Gly Ser Ala Ser Pro Phe Pro Phe Leu Thr Ala Leu Leu  
                                   100                                  105                                  110

Ser Leu Leu Asn Thr Leu Ala Gln Ile His Lys Gly Leu Cys Gly Gln  
           115                                  120                                  125

Leu Ala Ala Ile Leu Ala Ala Pro Gly Leu Gln Asn Tyr Phe Leu Gln  
           130                                  135                                  140

Cys Val Ala Pro Gly Ala Ala Pro His Leu Thr Pro Phe Ser Ala Trp  
           145                                  150                                  155                                  160

Ala Leu Arg His Glu Tyr His Leu Gln Tyr Leu Ala Leu Ala Leu Ala  
                                   165                                  170                                  175

Gln Lys Ala Ala Ala Leu Gln Pro Leu Pro Ala Thr His Ala Ala Leu  
                                   180                                  185                                  190

Tyr His Gly Met Ala Leu Ala Leu Leu Ser Arg Leu Leu Pro Gly Ser  
           195                                  200                                  205

Glu Tyr Leu Thr His Glu Leu Leu Leu Ser Cys Val Phe Arg Leu Glu  
           210                                  215                                  220

Phe Leu Pro Glu Arg Thr Ser Gly Gly Pro Glu Ala Ala Asp Phe Ser  
           225                                  230                                  235                                  240

Asp Gln Leu Ser Leu Gly Ser Ser Arg Val Pro Arg Cys Gly Gln Gly  
                                   245                                  250                                  255

Thr Leu Leu Ala Gln Ala Cys Gln Asp Leu Pro Ser Ile Arg Asn Cys  
                                   260                                  265                                  270

Tyr Leu Thr His Cys Ser Pro Ala Arg Ala Ser Leu Leu Ala Ser Gln  
           275                                  280                                  285

Ala Leu His Arg Gly Glu Leu Gln Arg Val Pro Thr Leu Leu Leu Pro  
           290                                  295                                  300

Met Pro Thr Glu Pro Leu Leu Pro Thr Asp Trp Pro Phe Leu His  
           305                                  310                                  315

<210> 239  
<211> 44  
<212> PRT  
<213> Homo sapiens

<400> 239  
Asp Val Glu Ser Arg Gly Pro Ser Ala Arg Cys Leu Pro Val Val Pro  
1 5 10 15  
Gly Ser Leu Leu Pro Gly Leu Glu Pro Ala Thr Lys Leu Met Pro Gly  
20 25 30  
Gly Leu Ala Pro Gly His Gly Ala Pro Val Arg Glu  
35 40

<210> 240  
<211> 45  
<212> PRT  
<213> Homo sapiens

<400> 240  
Leu Leu Leu Pro Leu Leu Ser Gln Pro Thr Leu Gly Ser Leu Trp Asp  
1 5 10 15  
Ser Leu Arg His Cys Ser Leu Leu Cys Asn Pro Leu Ser Cys Val Pro  
20 25 30  
Ala Leu Glu Ala Pro Pro Ser Leu Val Ser Leu Gly Cys  
35 40 45

<210> 241  
<211> 45  
<212> PRT  
<213> Homo sapiens

<400> 241  
Ser Gly Gly Cys Pro Arg Leu Ser Leu Ala Gly Ser Ala Ser Pro Phe  
1 5 10 15  
Pro Phe Leu Thr Ala Leu Leu Ser Leu Leu Asn Thr Leu Ala Gln Ile  
20 25 30  
His Lys Gly Leu Cys Gly Gln Leu Ala Ala Ile Leu Ala  
35 40 45

<210> 242  
<211> 44  
<212> PRT  
<213> Homo sapiens

<400> 242  
Ala Pro Gly Leu Gln Asn Tyr Phe Leu Gln Cys Val Ala Pro Gly Ala

137

1                      5                      10                      15  
 Ala Pro His Leu Thr Pro Phe Ser Ala Trp Ala Leu Arg His Glu Tyr  
                     20                      25                      30

His Leu Gln Tyr Leu Ala Leu Ala Leu Ala Gln Lys  
                     35                      40

<210> 243  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 243  
 Ala Ala Ala Leu Gln Pro Leu Pro Ala Thr His Ala Ala Leu Tyr His  
                     1                      5                      10                      15

Gly Met Ala Leu Ala Leu Leu Ser Arg Leu Leu Pro Gly Ser Glu Tyr  
                     20                      25                      30

Leu Thr His Glu Leu Leu Leu Ser Cys Val Phe Arg  
                     35                      40

<210> 244  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 244  
 Leu Glu Phe Leu Pro Glu Arg Thr Ser Gly Gly Pro Glu Ala Ala Asp  
                     1                      5                      10                      15

Phe Ser Asp Gln Leu Ser Leu Gly Ser Ser Arg Val Pro Arg Cys Gly  
                     20                      25                      30

Gln Gly Thr Leu Leu Ala Gln Ala Cys Gln Asp Leu  
                     35                      40

<210> 245  
 <211> 53  
 <212> PRT  
 <213> Homo sapiens

<400> 245  
 Pro Ser Ile Arg Asn Cys Tyr Leu Thr His Cys Ser Pro Ala Arg Ala  
                     1                      5                      10                      15

Ser Leu Leu Ala Ser Gln Ala Leu His Arg Gly Glu Leu Gln Arg Val  
                     20                      25                      30

Pro Thr Leu Leu Leu Pro Met Pro Thr Glu Pro Leu Leu Pro Thr Asp  
                     35                      40                      45

Trp Pro Phe Leu His  
50

<210> 246

<211> 25

<212> PRT

<213> Homo sapiens

<400> 246

Val Gly Ser Val Leu Gly Ala Phe Leu Thr Phe Pro Gly Leu Arg Leu  
1 5 10 15

Ala Gln Thr His Arg Asp Ala Leu Thr  
20 25

<210> 247

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (21)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (57)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 247

Leu Glu Cys Thr Asp Thr Ile Met Val His Cys Ser Leu Lys Leu Leu  
1 5 10 15

Ser Pro Ser Asp Xaa Ser His Ser Ala Ser Gln Val Ala Lys Thr Arg  
20 25 30

Gly Val His Xaa Thr Gln Leu Ile Phe Lys Val Phe Phe Val Xaa  
35 40 45

Met Gly Ser His Ser Thr Lys Tyr Xaa Ser Ile Arg Pro Gly Leu Leu  
50 55 60

Pro  
65

<210> 248  
<211> 14  
<212> PRT  
<213> Homo sapiens

<400> 248  
Glu Ser Ser Phe Val Pro Pro Ala Ala His Ser Ser Leu Cys  
1 5 10

<210> 249  
<211> 172  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (72)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 249  
Leu Leu Pro Gly Gln Gln Glu Ala Thr Gln Cys Val Glu Ala Gly Ala  
1 5 10 15  
Gly Glu Gly Ala Leu Thr Pro Met Cys Pro Cys Arg Gln Glu Gln Phe  
20 25 30  
Val Asp Leu Tyr Lys Glu Phe Glu Pro Ser Leu Val Asn Ser Thr Val  
35 40 45  
Tyr Ile Met Ala Met Ala Ile Gln Met Ala Pro Phe Ala Ile Asn Tyr  
50 55 60  
Lys Val Arg Pro Gly Pro Cys Xaa Asn Ile His Cys Leu Pro Thr Gln  
65 70 75 80  
Pro His Pro Met Lys Pro Ser Val Pro His Pro His Arg Ala Arg Pro  
85 90 95  
Ser Trp Arg Ala Cys Pro Arg Thr Ser Pro Trp Cys Gly Val Trp Gln  
100 105 110  
Phe His Ser Trp Pro Ser Leu Ala Cys Ser Ser Ala Pro Arg Pro Thr  
115 120 125  
Ser Thr Ala Ser Leu Ala Ser Trp Thr Ser Leu Trp Ser Ser Ser Trp  
130 135 140  
Ser Leu Pro Arg Ser Cys Ser Trp Thr Ser Ala Trp Arg Ser Trp Pro  
145 150 155 160

140

Thr Ala Ser Cys Ser Ser Ser Trp Gly Pro Arg Ser  
                   165                          170

<210> 250  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<400> 250  
 Leu Leu Pro Gly Gln Gln Glu Ala Thr Gln Cys Val Glu Ala Gly Ala  
   1                  5                          10                          15

Gly Glu Gly Ala Leu Thr Pro Met Cys Pro Cys Arg Gln Glu Gln Phe  
                   20                          25                          30

Val Asp Leu Tyr Lys Glu Phe Glu Pro Ser Leu Val Asn  
           35                          40                          45

<210> 251  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (27)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 251  
 Ser Thr Val Tyr Ile Met Ala Met Ala Ile Gln Met Ala Pro Phe Ala  
   1                  5                          10                          15

Ile Asn Tyr Lys Val Arg Pro Gly Pro Cys Xaa Asn Ile His Cys Leu  
                   20                          25                          30

Pro Thr Gln Pro His Pro Met Lys Pro Ser Val Pro  
           35                          40

<210> 252  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<400> 252  
 His Pro His Arg Ala Arg Pro Ser Trp Arg Ala Cys Pro Arg Thr Ser  
   1                  5                          10                          15

Pro Trp Cys Gly Val Trp Gln Phe His Ser Trp Pro Ser Leu Ala Cys  
                   20                          25                          30

Ser Ser Ala Pro Arg Pro Thr Ser Thr Ala



141

35

40

&lt;210&gt; 253

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 253

Ser Leu Ala Ser Trp Thr Ser Leu Trp Ser Ser Ser Trp Ser Leu Pro  
 1 5 10 15

Arg Ser Cys Ser Trp Thr Ser Ala Trp Arg Ser Trp Pro Thr Ala Ser  
 20 25 30

Cys Ser Ser Ser Trp Gly Pro Arg Ser  
 35 40

&lt;210&gt; 254

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 254

Thr Arg Asn Ile Leu Ser Phe Ile Lys Cys Val Ile His Asn Phe Trp  
 1 5 10 15

Ile Pro Lys Glu Ser Asn Glu Ile Thr Ile Ile Ile Asn Pro Tyr Arg  
 20 25 30

Glu Thr Val Cys Phe Ser Val Glu Pro Val Lys Lys Ile Phe Asn Tyr  
 35 40 45

&lt;210&gt; 255

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 255

Leu Val Val Leu Phe Ala Ser Ser Asn Ser Arg Tyr Leu Lys Tyr Phe  
 1 5 10 15

Phe Leu Val Pro Leu Ile Leu Gly Ser Ala Trp  
 20 25

&lt;210&gt; 256

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

142

&lt;400&gt; 256

His Glu Trp Lys Cys Lys Gln Lys Tyr Ser Glu Gly Ser Gly Asn Thr  
1 5 10 15

Arg Ile Gly Asn  
20

&lt;210&gt; 257

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 257

Leu Leu Pro Leu Cys Phe Leu Gly Pro Arg Gln Val Leu Glu Glu Phe  
1 5 10 15

Pro Ser Ile Val  
20

&lt;210&gt; 258

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 258

Pro Thr Arg Pro Ser Lys His Gln Glu Ala Gly Ser  
1 5 10

&lt;210&gt; 259

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (39)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 259

Gly Gln Gly Pro Ala Gly Arg Trp Val Arg Arg Leu Pro Cys Ser Arg  
1 5 10 15

Arg Ala Gly Gly Glu Arg Gly Pro His Trp Gly Val Trp Ala Gly Pro  
20 25 30

Gln Met Ser Cys Gly Leu Xaa Phe Gly Pro  
35 40

&lt;210&gt; 260

&lt;211&gt; 193

143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 260

Trp Arg Thr Gln Gly Pro Met Val Leu Leu Trp Val Val Thr Cys Pro  
 1 5 10 15  
 Ala Thr Met Leu Thr Glu Pro Gln Asn Pro His Leu Ile Gly Phe Val  
 20 25 30  
 Ala Tyr Ser Gly Pro Ser His Thr Thr Gln Pro His Lys Tyr Trp Leu  
 35 40 45  
 Leu Leu Asp Gly Gln Ala Asp Pro Ala Ala Ala Glu Gly Pro Val Lys  
 50 55 60  
 Arg Lys Ala Ala Ser Val Val Trp Trp Pro Gln Ala Leu Arg His Leu  
 65 70 75 80  
 Ser Leu Leu Val His Cys Trp Glu Glu Ser Tyr Glu Met Asn Ile Gly  
 85 90 95  
 Cys Gln Ser Leu Trp Ala Gly Gly Leu Ala Ser Ser Gly Asn Gly Trp  
 100 105 110  
 Asp Leu Gly Val Ala Phe Arg Arg Asp Thr Cys Met Ser Ser Ser Ser  
 115 120 125  
 Leu His Trp Lys Glu Phe Lys Tyr Ala Pro Gly Ser Leu His Tyr Phe  
 130 135 140  
 Ala Leu Ser Phe Val Leu Ile Leu Thr Glu Ile Cys Leu Val Ser Ser  
 145 150 155 160  
 Gly Met Gly Phe Pro Gln Glu Gly Lys His Phe Ser Val Leu Gly Ser  
 165 170 175  
 Pro Asp Cys Ser Leu Trp Gly Arg Asp Glu His Val Pro Arg Glu Phe  
 180 185 190

Ala

&lt;210&gt; 261

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 261

Trp Arg Thr Gln Gly Pro Met Val Leu Leu Trp Val Val Thr Cys Pro  
 1 5 10 15  
 Ala Thr Met Leu Thr Glu Pro Gln Asn Pro His Leu Ile Gly Phe Val  
 20 25 30

144

Ala Tyr Ser Gly Pro Ser His Thr Thr Gln  
 35 40

<210> 262  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<400> 262  
 Pro His Lys Tyr Trp Leu Leu Leu Asp Gly Gln Ala Asp Pro Ala Ala  
 1 5 10 15

Ala Glu Gly Pro Val Lys Arg Lys Ala Ala Ser Val Val Trp Trp Pro  
 20 25 30

Gln Ala Leu Arg His Leu Ser Leu Leu  
 35 40

<210> 263  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<400> 263  
 Val His Cys Trp Glu Glu Ser Tyr Glu Met Asn Ile Gly Cys Gln Ser  
 1 5 10 15

Leu Trp Ala Gly Gly Leu Ala Ser Ser Gly Asn Gly Trp Asp Leu Gly  
 20 25 30

Val Ala Phe Arg Arg Asp Thr Cys Met  
 35 40

<210> 264  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 264  
 Ser Ser Ser Ser Leu His Trp Lys Glu Phe Lys Tyr Ala Pro Gly Ser  
 1 5 10 15

Leu His Tyr Phe Ala Leu Ser Phe Val Leu Ile Leu Thr Glu Ile Cys  
 20 25 30

Leu Val Ser Ser Gly Met Gly Phe Pro Gln Glu Gly  
 35 40

<210> 265  
 <211> 25

145

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 265

Lys His Phe Ser Val Leu Gly Ser Pro Asp Cys Ser Leu Trp Gly Arg  
 1 5 10 15

Asp Glu His Val Pro Arg Glu Phe Ala  
 20 25

&lt;210&gt; 266

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 266

Ile Ala Gln Gly Thr Val Pro Leu Thr Lys Arg Gly Val Gln Ser Ser  
 1 5 10 15

Gly Pro Asp Tyr Pro Glu Gly Thr Leu Thr Pro Leu Pro Arg Gly  
 20 25 30

&lt;210&gt; 267

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 267

Ile Ala Gln Gly Thr Val Pro Leu Thr Lys Arg Gly Val Gln Ser Ser  
 1 5 10 15

Gly Pro Asp Tyr Pro Glu Gly Thr Leu Thr Pro Leu Pro Arg Gly  
 20 25 30

&lt;210&gt; 268

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 268

Asp Cys Leu Tyr Leu Ala Leu Ser Phe Pro Trp His Cys His Cys His  
 1 5 10 15

His His Pro Pro Ser Gly Ser Leu Leu Tyr Pro Phe  
 20 25

&lt;210&gt; 269

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

146

&lt;400&gt; 269

Ala Ser Leu Pro Pro Ser Arg Ser Arg Pro Leu Ala Asn Met Ala Leu  
 1 5 10 15

Val Pro Cys Gln Val Leu Arg Met Ala Ile Leu Leu Ser Tyr Cys Ser  
 20 25 30

Ile Leu Cys Asn Tyr Lys Ala Ile Glu Met Pro Ser His Gln Thr Tyr  
 35 40 45

Gly Gly Ser Trp Lys Phe Leu Thr Phe Ile Asp Leu Val Ile Gln Ala  
 50 55 60

Val Phe Phe Gly Ile Cys Val Leu Thr Asp Leu Ser Ser Leu Leu Thr  
 65 70 75 80

Arg Gly Ser Gly Asn Gln Glu Gln Glu Arg Gln Leu Lys Lys Leu Ile  
 85 90 95

Ser Leu Arg Asp Trp  
 100

&lt;210&gt; 270

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 270

Met Ser Arg Ser Ser Arg Ile Ser Gly Leu Ser Cys Pro Trp Leu Leu  
 1 5 10 15

&lt;210&gt; 271

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 271

Asp His Trp Pro Ala Gly Phe Leu Pro Pro Ala Pro Gly Leu Lys Phe  
 1 5 10 15

Pro Val Ala Leu Glu Val Phe Arg Lys Val Leu Pro Ala Val Cys Pro  
 20 25 30

Thr Asp Cys Ser Gly Ser Ala Gly Lys Glu Arg Asn Ser  
 35 40 45

&lt;210&gt; 272

&lt;211&gt; 47

&lt;212&gt; PRT

147

&lt;213&gt; Homo sapiens

&lt;400&gt; 272

Glu Glu Ile Ala Thr Ser Ile Glu Pro Ile Arg Asp Phe Leu Ala Ile  
1 5 10 15  
Val Phe Phe Ala Ser Ile Gly Leu His Val Phe Pro Thr Phe Val Ala  
20 25 30  
Tyr Glu Leu Thr Val Leu Val Phe Leu Thr Leu Ser Val Val Val  
35 40 45

&lt;210&gt; 273

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 273

Tyr Cys Asn Leu Gln Cys Arg  
1 5

&lt;210&gt; 274

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 274

Ser Ala Leu Ile Gly Asn Pro Lys Gly Cys Phe Gly Cys Phe Ser Pro  
1 5 10 15  
Val Val Leu Arg Glu Trp Ser Val Glu Ser Trp Lys Ser Leu Arg Pro  
20 25 30  
Phe Gln Ala Ile Cys Lys Leu Lys Thr Asn Phe Arg  
35 40

&lt;210&gt; 275

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 275

His Glu Ala Ala Leu Arg Gly Pro  
1 5

&lt;210&gt; 276

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 276

148

Ser Asn Ala Ala Gly Asn Val Val Arg Ala Phe Leu Tyr Ile Asn His  
 1 5 10 15

Leu Lys Leu Gly Cys Lys Val Gly Leu Ala  
 20 25

&lt;210&gt; 277

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 277

Asn Trp Ala Val Leu Asn Met Leu Leu Ser Lys Gly Lys Ile Thr Ile  
 1 5 10 15

Phe Leu Gly Pro Leu Glu Cys Gly Ser  
 20 25

&lt;210&gt; 278

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 278

Pro Ser His Gln Thr Arg Lys Gly Lys Ser Ala Lys Leu Leu Asp Arg  
 1 5 10 15

Pro Pro Glu Ala Leu Arg Met Lys Ile Ile Thr Thr Thr Leu Leu Leu  
 20 25 30

Ala Cys His Leu Gln Leu Glu Val Gly Val Val Val Gly Gly Glu Val  
 35 40 45

Asp

&lt;210&gt; 279

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 279

Phe Gln Ala Ser Ser Ala Asn Asn Gln Gln Asn Trp Gly Ser Gln Pro  
 1 5 10 15

Ile Ala Gln Gln Pro Leu Gln Gln Gly Gly Asp Tyr Ser Gly Asn Tyr  
 20 25 30

Gly Tyr Asn Asn Asp Asn Gln Glu Phe Tyr Gln Asp Thr Tyr Gly Gln  
 35 40 45

Gln Trp Lys



50

<210> 280  
 <211> 264  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (2)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (6)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (14)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 280  
 Trp Xaa Pro Leu Leu Xaa Thr Ser Gly Ser Pro Gly Leu Xaa Gly Phe  
   1                  5                  10                  15  
 Gly Thr Arg Met Asn Gly Lys Glu Ile Glu Gly Glu Glu Ile Glu Ile  
                   20                  25                  30  
 Val Leu Ala Lys Pro Pro Asp Lys Lys Arg Lys Glu Arg Gln Ala Ala  
                   35                  40                  45  
 Arg Gln Ala Ser Arg Ser Thr Ala Tyr Glu Asp Tyr Tyr Tyr His Pro  
   50                  55                  60  
 Pro Pro Arg Met Pro Pro Pro Ile Arg Gly Arg Gly Arg Gly Gly Gly  
   65                  70                  75                  80  
 Arg Gly Gly Tyr Gly Tyr Pro Pro Asp Tyr Tyr Gly Tyr Glu Asp Tyr  
                   85                  90                  95  
 Tyr Asp Asp Tyr Tyr Gly Tyr Asp Tyr His Asp Tyr Arg Gly Gly Tyr  
                   100                  105                  110  
 Glu Asp Pro Tyr Tyr Gly Tyr Asp Asp Gly Tyr Ala Val Arg Gly Arg  
   115                  120                  125  
 Gly Gly Gly Arg Gly Gly Arg Gly Ala Pro Pro Pro Pro Arg Gly Arg  
   130                  135                  140  
 Gly Ala Pro Pro Pro Arg Gly Arg Ala Gly Tyr Ser Gln Arg Gly Ala  
   145                  150                  155                  160  
 Pro Leu Gly Pro Pro Arg Gly Ser Arg Gly Gly Arg Gly Gly Pro Ala

150

	165		170		175
Gln Gln Gln Arg Gly Arg Gly Ser Arg Gly Ser Arg Gly Asn Arg Gly					
	180		185		190
Gly Asn Val Gly Gly Lys Arg Lys Ala Asp Gly Tyr Asn Gln Pro Asp					
	195		200		205
Ser Lys Arg Arg Gln Pro Thr Thr Asn Arg Thr Gly Val Pro Asn Pro					
	210		215		220
Ser Leu Ser Ser Arg Phe Ser Lys Val Val Thr Ile Leu Val Thr Met					
	225		230		235
Val Thr Ile Met Thr Thr Arg Asn Phe Ile Arg Ile Leu Met Gly Asn					
	245		250		255
Ser Gly Ser Arg Gln Val Arg Ala					
	260				

&lt;210&gt; 281

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 281

Arg Met Asn Gly Lys Glu Ile Glu Gly Glu Glu Ile Glu Ile Val Leu
1 5 10 15

Ala Lys Pro Pro Asp Lys Lys Arg Lys Glu Arg
20 25

&lt;210&gt; 282

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 282

Tyr Tyr His Pro Pro Pro Arg Met Pro Pro Pro Ile Arg Gly Arg Gly
1 5 10 15

Arg Gly Gly Gly Arg Gly Gly Tyr Gly
20 25

&lt;210&gt; 283

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 283

Asp Tyr Arg Gly Gly Tyr Glu Asp Pro Tyr Tyr Gly Tyr Asp Asp Gly
1 5 10 15

Tyr Ala Val Arg Gly Arg Gly Gly Arg  
20 25

<210> 284  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 284  
Pro Pro Pro Arg Gly Arg Ala Gly Tyr Ser Gln Arg Gly Ala Pro Leu  
1 5 10 15

Gly Pro Pro Arg Gly Ser Arg Gly Gly Arg Gly Gly  
20 25

<210> 285  
<211> 35  
<212> PRT  
<213> Homo sapiens

<400> 285  
Ala Asp Gly Tyr Asn Gln Pro Asp Ser Lys Arg Arg Gln Pro Thr Thr  
1 5 10 15

Asn Arg Thr Gly Val Pro Asn Pro Ser Leu Ser Ser Arg Phe Ser Lys  
20 25 30

Val Val Thr  
35

<210> 286  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 286  
Leu Gln Ile Pro Pro Ser Ser Gln Ser Leu Gly Leu Lys Asn Ala Asp  
1 5 10 15

Ser Ser Ile

<210> 287  
<211> 129  
<212> PRT  
<213> Homo sapiens

<400> 287  
Gly Gly Pro Pro Glu Ser Ala Pro Trp Leu Pro Ala Val Leu Arg Ala  
1 5 10 15

152

Pro Val Leu Thr Ser Arg Cys Ala Ser Ser Asp Ser Glu Gly Pro Val  
                   20                  25                  30  
 Trp Phe Cys Gln Pro Gly Ser Gly Pro Ser Ser Thr Glu Met Ser Cys  
                   35                  40                  45  
 His Cys Ile Leu Gly Pro Gly Ser Ser Cys Leu Cys Val Leu Arg Gly  
                   50                  55                  60  
 Ser Met Trp Thr Pro Ser Val Pro Gly Trp Pro Gln Pro Ala Lys Glu  
                   65                  70                  75                  80  
 Thr Gly Ala Ser Ser Cys Ser Val Phe Ser Ala Asn Asn Gly Ser Cys  
                   85                  90                  95  
 Pro Leu Pro Leu His Asn His Gln Arg Gln Ala Ser Leu Asp Thr Gly  
                   100                  105                  110  
 Leu Ser Leu Glu His Val Pro Gly Glu Ser Tyr Phe Tyr Ser Pro Val  
                   115                  120                  125  
 Gly

<210> 288  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 288  
 Ser Ser Asp Ser Glu Gly Pro Val Trp Phe Cys Gln Pro Gly Ser Gly  
   1                  5                  10                  15  
 Pro Ser Ser Thr Glu Met Ser Cys His Cys Ile Leu Gly Pro Gly Ser  
                   20                  25                  30  
 Ser Cys

<210> 289  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 289  
 Trp Thr Pro Ser Val Pro Gly Trp Pro Gln Pro Ala Lys Glu Thr Gly  
   1                  5                  10                  15  
 Ala Ser Ser Cys Ser Val Phe Ser Ala Asn Asn Gly  
                   20                  25

<210> 290  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 290  
Gln Arg Gln Ala Ser Leu Asp Thr Gly Leu Ser Leu Glu His Val Pro  
1 5 10 15

Gly Glu Ser Tyr Phe  
20

<210> 291  
<211> 29  
<212> PRT  
<213> Homo sapiens

<400> 291  
Ser Ser Ser Leu Val Leu Thr Ile Arg Ser Gln Thr Leu Phe Leu Ala  
1 5 10 15

Ser Phe Ile His Ser Thr Ser Ile Phe Cys Ala Leu Asn  
20 25

<210> 292  
<211> 12  
<212> PRT  
<213> Homo sapiens

<400> 292  
Cys Cys Cys Arg Leu Gly Leu Ser Gly Pro Lys Cys  
1 5 10

<210> 293  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 293  
Arg Ala Phe Trp Gly Leu Gly Ala Leu Gln Leu Leu Asp Leu Ser Ala  
1 5 10 15

Asn Gln Leu Glu Ala Leu  
20

<210> 294  
<211> 34  
<212> PRT  
<213> Homo sapiens

<400> 294

154

His Ala Ser Gly Arg Arg Thr Gly Ser Ala Asp Asp Gly Leu Gln Gly  
 1 5 10 15

Arg Thr Gly Ser Gly Pro Pro Thr Ala Gly Ala Gly Gly Gly Gly Ala  
 20 25 30

Ala Pro

<210> 295

<211> 205

<212> PRT

<213> Homo sapiens

<400> 295

Val Ser Ala Ala Ala Gly Ala Arg Leu Ala Pro Arg Ala Pro Gly Ala  
 1 5 10 15

Pro Ala Gly Cys Arg Pro Met Arg Gly Cys Ala Ala Arg Ala Ala Ala  
 20 25 30

Arg Lys Ser Leu Val Pro Val Leu Pro Ala Gly Trp Arg Ser Gly Pro  
 35 40 45

Ala Ala Ala Ala Arg Pro Gly Pro Arg Arg Leu Ala His Ala Pro Ser  
 50 55 60

Ala Ala Arg Ser Arg Ala Gly Pro Gly Ala Val Ala Arg Pro Leu Pro  
 65 70 75 80

Arg Arg His Leu Ala Ala Ala His Gly Arg Gly Cys Gly Pro Ala Ala  
 85 90 95

Ala Arg Ala Gly Ala Gly Ser Gly Pro Gly Ala Arg Arg Ala Ala Arg  
 100 105 110

Val Pro Thr Ala Gly Arg Pro Pro Gly Thr His Val His Thr Ser Gly  
 115 120 125

Gln Ser Gly Ala Pro Arg Asp Pro Glu Gly Glu Ala Leu Ala Asp Thr  
 130 135 140

Trp Ala Gln Thr Gly Gln Gly Asp Ser Ser Ser Asn Ser Ser Ser Ser  
 145 150 155 160

Gly Arg Gly Arg Asp Gln Glu Gly Pro Arg Met Gly Ala Ala Pro Pro  
 165 170 175

Pro Pro Ala Pro Ala Val Gly Gly Pro Leu Pro Val Arg Pro Trp Ser  
 180 185 190

Pro Ser Ser Ala Glu Pro Val Leu Arg Pro Asp Ala Trp  
 195 200 205

<210> 296  
 <211> 368  
 <212> PRT  
 <213> Homo sapiens

<400> 296

Thr Arg Pro Ala Ala Glu Arg Ala Pro Arg Thr Thr Gly Ser Arg Asp  
 1 5 10 15

Ala Gln Ala Ala Gly Leu Pro Pro Arg Val Pro Gly Ala Gly Gly Leu  
 20 25 30

Pro Pro Cys Gly Ala Leu Pro Gly Arg Gly Leu Gly Arg Cys Cys Cys  
 35 40 45

Cys Cys Cys Cys Cys Arg Leu Gly Leu Ser Gly Pro Lys Cys Arg Pro  
 50 55 60

Gly Pro Arg Pro Arg Gly Pro Trp Ala Pro Arg Thr Ala Pro Arg Cys  
 65 70 75 80

Ala Arg Ala Cys Arg Glu Ala Cys Gln Leu Ser Ala Leu Ser Leu Pro  
 85 90 95

Ala Val Pro Pro Gly Leu Ser Leu Arg Leu Arg Ala Leu Leu Leu Asp  
 100 105 110

His Asn Arg Val Arg Ala Leu Pro Pro Gly Ala Phe Ala Gly Ala Gly  
 115 120 125

Ala Leu Gln Arg Leu Asp Leu Arg Glu Asn Gly Leu His Ser Val His  
 130 135 140

Val Arg Ala Phe Trp Gly Leu Gly Ala Leu Gln Leu Leu Asp Leu Ser  
 145 150 155 160

Ala Asn Gln Leu Glu Ala Leu Ala Pro Gly Thr Phe Ala Pro Leu Arg  
 165 170 175

Ala Leu Arg Asn Leu Ser Leu Ala Gly Asn Arg Leu Ala Arg Leu Glu  
 180 185 190

Pro Ala Ala Leu Gly Ala Leu Pro Leu Leu Arg Ser Leu Ser Leu Gln  
 195 200 205

Asp Asn Glu Leu Ala Ala Leu Ala Pro Gly Leu Leu Gly Arg Leu Pro  
 210 215 220

Ala Leu Asp Ala Leu His Leu Arg Gly Asn Pro Trp Gly Cys Gly Cys  
 225 230 235 240

Ala Leu Arg Pro Leu Cys Ala Trp Leu Arg Arg His Pro Leu Pro Ala  
 245 250 255

156

Ser Glu Ala Glu Thr Val Leu Cys Val Trp Pro Gly Arg Leu Thr Leu  
                   260                                  265                                  270

Ser Pro Leu Thr Ala Phe Ser Asp Ala Ala Phe Ser His Cys Ala Gln  
                   275                                  280                                  285

Pro Leu Ala Leu Arg Asp Leu Ala Arg Gly Leu His Ala Arg Ala Gly  
                   290                                  295                                  300

Leu Leu Pro Arg Gln Pro Gly Phe Leu Pro Gly Ala Gly Leu Trp Ala  
                   305                                  310                                  315                                  320

His Arg Leu Pro Cys Ala Pro Pro Pro Pro Pro His Arg Arg Pro Pro  
                                   325                                  330                                  335

Pro Ala Glu Thr Val Gln Thr Arg Thr Pro Ile Pro Thr Pro Thr Ala  
                   340                                  345                                  350

Val Pro Arg Pro Arg Thr Arg Gly Ala Pro Ser Ala Ala Ala Gln Ala  
                   355                                  360                                  365

<210> 297  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 297  
 Gly Cys Arg Pro Met Arg Gly Cys Ala Ala Arg Ala Ala Arg Lys  
   1                                  5                                  10                                  15

Ser Leu Val Pro Val Leu Pro Ala Gly Trp Arg Ser Gly Pro Ala Ala  
                   20                                  25                                  30

Ala Ala Arg Pro Gly Pro Arg Arg Leu Ala His Ala Pro Ser Ala  
                   35                                  40                                  45

<210> 298  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 298  
 Pro Gly Ala Val Ala Arg Pro Leu Pro Arg Arg His Leu Ala Ala Ala  
   1                                  5                                  10                                  15

His Gly Arg Gly Cys Gly Pro Ala Ala Ala Arg Ala Gly Ala  
                   20                                  25                                  30

<210> 299



<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 299  
Ser Gly Gln Ser Gly Ala Pro Arg Asp Pro Glu Gly Glu Ala Leu Ala  
1 5 10 15

Asp Thr Trp Ala Gln Thr Gly Gln  
20

<210> 300  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 300  
Pro Pro Ala Pro Ala Val Gly Gly Pro Leu Pro Val Arg Pro Trp Ser  
1 5 10 15

Pro Ser Ser Ala Glu Pro Val  
20

<210> 301  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 301  
Ala Pro Arg Thr Thr Gly Ser Arg Asp Ala Gln Ala Ala Gly Leu Pro  
1 5 10 15

Pro Arg Val Pro Gly Ala Gly Gly Leu Pro  
20 25

<210> 302  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 302  
Gly Pro Arg Pro Arg Gly Pro Trp Ala Pro Arg Thr Ala Pro Arg Cys  
1 5 10 15

Ala Arg Ala Cys Arg Glu  
20

<210> 303  
<211> 31  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 303

Ala Val Pro Pro Gly Leu Ser Leu Arg Leu Arg Ala Leu Leu Leu Asp  
1 5 10 15

His Asn Arg Val Arg Ala Leu Pro Pro Gly Ala Phe Ala Gly Ala  
20 25 30

&lt;210&gt; 304

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 304

Leu Gly Ala Leu Gln Leu Leu Asp Leu Ser Ala Asn Gln Leu Glu Ala  
1 5 10 15

Leu Ala Pro Gly Thr Phe Ala Pro  
20

&lt;210&gt; 305

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 305

Pro Pro Gly Ala Phe Ala Gly Ala Gly Ala Leu Gln Arg Leu Asp Leu  
1 5 10 15

Arg Glu Asn Gly Leu His Ser Val His Val Arg Ala Phe Trp Gly Leu  
20 25 30

Gly Ala Leu Gln  
35

&lt;210&gt; 306

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 306

Arg Asn Leu Ser Leu Ala Gly Asn Arg Leu Ala Arg Leu Glu Pro Ala  
1 5 10 15

Ala Leu Gly Ala Leu Pro Leu Leu Arg Ser Leu Ser  
20 25

&lt;210&gt; 307

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 307

Leu Pro Ala Leu Asp Ala Leu His Leu Arg Gly Asn Pro Trp Gly Cys  
1 5 10 15

Gly Cys Ala Leu Arg Pro Leu Cys Ala Trp  
20 25

&lt;210&gt; 308

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 308

Thr Val Leu Cys Val Trp Pro Gly Arg Leu Thr Leu Ser Pro Leu Thr  
1 5 10 15

Ala Phe Ser Asp Ala Ala Phe Ser His Cys Ala Gln Pro Leu Ala Leu  
20 25 30

Arg Asp

&lt;210&gt; 309

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 309

Leu His Ala Arg Ala Gly Leu Leu Pro Arg Gln Pro Gly Phe Leu Pro  
1 5 10 15

Gly Ala Gly Leu Trp Ala His Arg  
20

&lt;210&gt; 310

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 310

Thr Val Gln Thr Arg Thr Pro Ile Pro Thr Pro Thr Ala Val Pro Arg  
1 5 10 15

Pro Arg Thr Arg Gly Ala Pro Ser  
20

&lt;210&gt; 311

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

160

&lt;400&gt; 311

His Ala Ser Gly Arg Pro Asp Arg Ser Ser Ala Pro Ile Gly Asn Ser  
 1 5 10 15

Gly Leu Pro Cys Pro Asp Leu Glu Pro Leu Gly Gly Leu Gln Ser Lys  
 20 25 30

Cys Arg Leu Cys Ala Pro Thr Glu Ala Arg Gly Leu Trp Ser Arg Ser  
 35 40 45

Leu Cys Ser Asp Arg Cys Asp Thr Trp Arg Ser  
 50 55

&lt;210&gt; 312

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 312

Gly Leu Pro Cys Pro Asp Leu Glu Pro Leu Gly Gly Leu Gln Ser Lys  
 1 5 10 15

Cys Arg Leu Cys Ala Pro Thr Glu Ala Arg Gly Leu Trp  
 20 25

&lt;210&gt; 313

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 313

Gln Glu Trp Glu Ser Glu Leu Gly Glu Arg Arg Lys Pro Leu Gln Ala  
 1 5 10 15

&lt;210&gt; 314

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 314

Cys Gln Ser Ser Asn Leu Ile Phe Phe Gln Phe Val Asn Ile Leu Phe  
 1 5 10 15

Asn Leu Met Met Asp Ile Leu Val Asp Phe Ser Ile Thr Lys Met Pro  
 20 25 30

Ile Asn Ser Ile Phe Ser Leu Tyr Phe Cys Tyr Glu Ile Ile  
 35 40 45

161

<210> 315  
 <211> 134  
 <212> PRT  
 <213> Homo sapiens

<400> 315

Gly	Pro	Val	Trp	Leu	Phe	Cys	Phe	Leu	Thr	Leu	Cys	Arg	Lys	Pro	Ser
1				5					10					15	
Gln	Leu	Phe	Ser	Gln	Glu	Asn	Ser	Cys	Met	Asp	Val	Ala	Gly	Gly	Val
			20					25					30		
Thr	Thr	Cys	Leu	Pro	Pro	Trp	Phe	Ser	Arg	Gly	Ala	Pro	Ala	Gln	Met
		35					40					45			
Ser	Gln	Trp	Pro	Pro	Ser	Ser	Asp	His	Gly	Ala	Val	Arg	Ala	Gly	Arg
	50					55					60				
Asp	Ser	Arg	Val	Gly	Pro	Val	Gln	Pro	Ser	His	Leu	Thr	Cys	Glu	Gly
65					70					75				80	
Gly	Lys	Glu	Glu	Arg	Glu	Lys	Asn	Lys	Lys	Ala	Glu	Val	Asn	Pro	Pro
				85					90					95	
Thr	Gly	Met	Gly	Leu	Ala	Asn	Arg	Ile	Pro	Arg	Asp	Asp	Ile	Thr	Leu
			100					105					110		
Lys	Leu	Arg	Asn	Gln	Gly	Lys	Leu	Arg	Thr	Lys	Glu	Asn	Arg	Thr	Gln
	115						120					125			
Ser	Ala	Lys	Arg	His	Pro										
	130														

<210> 316  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<400> 316

Val	Ala	Cys	Lys	Pro	Glu	Asn	Arg	Thr	Lys	Thr	His	Phe	Ala	Ser	Ser
1				5					10					15	
Pro	Ala	Cys	Asp	Gly	His	Ala	Leu	Gly	Gly	Gln	Val	Gly	Phe	Ala	Ile
			20					25					30		
Cys	Phe	Leu	Ser	Cys	Leu	Phe	Pro	Pro	Met						
	35						40								

<210> 317  
 <211> 40  
 <212> PRT

162

&lt;213&gt; Homo sapiens

&lt;400&gt; 317

Ser His Pro Met Pro Asn Thr Pro Gln Lys Gln Leu Leu Phe Ser Glu  
 1 5 10 15

Asp Asn Glu Leu Leu Val Ser Leu Arg Thr Gly Arg Lys Pro Thr Leu  
 20 25 30

Gln Ala Ala Leu Arg Val Thr Gly  
 35 40

&lt;210&gt; 318

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 318

Glu Gly Asp Pro Arg Gly Arg Pro Arg Pro Arg Pro Leu Gly Pro Pro  
 1 5 10 15

Pro Gln Leu Thr Leu Pro Thr Ala Leu Xaa Asp Ile Leu Arg Gln Val  
 20 25 30

Arg Ala Pro Gly Leu Arg Leu Ser Arg Ala Leu Glu Val Gly Arg Lys  
 35 40 45

Gly Ser Pro Ile Phe Lys Ile Gln Ile Tyr Leu  
 50 55

&lt;210&gt; 319

&lt;211&gt; 250

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (145)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 319

Ala His Arg Leu Gln Ile Arg Leu Leu Thr Trp Asp Val Lys Asp Thr  
 1 5 10 15

Leu Leu Arg Leu Arg His Pro Leu Gly Glu Ala Tyr Ala Thr Lys Ala  
 20 25 30

Arg Ala His Gly Leu Glu Val Glu Pro Ser Ala Leu Glu Gln Gly Phe

163

35	40	45
Arg Gln Ala Tyr Arg Ala Gln Ser His Ser Phe Pro Asn Tyr Gly Leu		
50	55	60
Ser His Gly Leu Thr Ser Arg Gln Trp Trp Leu Asp Val Val Leu Gln		
65	70	75
Thr Phe His Leu Ala Gly Val Gln Asp Ala Gln Ala Val Ala Pro Ile		
85	90	95
Ala Glu Gln Leu Tyr Lys Asp Phe Ser His Pro Cys Thr Trp Gln Val		
100	105	110
Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu Cys Arg Thr Arg Gly Leu		
115	120	125
Arg Leu Ala Val Ile Ser Asn Phe Asp Arg Arg Leu Glu Gly Ile Leu		
130	135	140
Xaa Gly Leu Gly Leu Arg Glu His Phe Asp Phe Val Leu Thr Ser Glu		
145	150	155
Ala Ala Gly Trp Pro Lys Pro Asp Pro Arg Ile Phe Gln Glu Ala Leu		
165	170	175
Arg Leu Ala His Met Glu Pro Val Val Ala Ala His Val Gly Asp Asn		
180	185	190
Tyr Leu Cys Asp Tyr Gln Gly Pro Arg Ala Val Gly Met His Ser Phe		
195	200	205
Leu Val Val Gly Pro Gln Ala Leu Asp Pro Val Val Arg Asp Ser Val		
210	215	220
Pro Lys Glu His Ile Leu Pro Ser Leu Ala His Leu Leu Pro Ala Leu		
225	230	235
Asp Cys Leu Glu Gly Ser Thr Pro Gly Leu		
245	250	

&lt;210&gt; 320

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 320

Ile Arg Leu Leu Thr Trp Asp Val Lys Asp Thr Leu Leu Arg Leu Arg
1 5 10 15

His Pro Leu Gly Glu Ala Tyr Ala Thr Lys Ala
20 25

164

<210> 321  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 321  
Leu Glu Gln Gly Phe Arg Gln Ala Tyr Arg Ala Gln Ser His Ser Phe  
1 5 10 15  
Pro Asn Tyr Gly Leu Ser His Gly  
20

<210> 322  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 322  
His Leu Ala Gly Val Gln Asp Ala Gln Ala Val Ala Pro Ile Ala Glu  
1 5 10 15  
Gln Leu Tyr Lys Asp Phe Ser His Pro Cys  
20 25

<210> 323  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 323  
Val Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu Cys Arg Thr Arg Gly  
1 5 10 15  
Leu Arg Leu Ala Val Ile Ser  
20

<210> 324  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 324  
Arg Glu His Phe Asp Phe Val Leu Thr Ser Glu Ala Ala Gly Trp Pro  
1 5 10 15  
Lys Pro Asp Pro Arg Ile Phe Gln Glu Ala  
20 25

<210> 325  
<211> 28  
<212> PRT



165

&lt;213&gt; Homo sapiens

&lt;400&gt; 325

Glu Pro Val Val Ala Ala His Val Gly Asp Asn Tyr Leu Cys Asp Tyr  
1 5 10 15

Gln Gly Pro Arg Ala Val Gly Met His Ser Phe Leu  
20 25

&lt;210&gt; 326

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 326

Val Val Arg Asp Ser Val Pro Lys Glu His Ile Leu Pro Ser Leu Ala  
1 5 10 15

His Leu Leu Pro Ala Leu Asp  
20

&lt;210&gt; 327

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 327

Ile Arg Lys Leu Gly Pro Gly Leu Ala Pro Cys Ser Cys Arg Ser Gly  
1 5 10 15

Gln Val Phe Pro Arg Val  
20

&lt;210&gt; 328

&lt;211&gt; 241

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 328

Lys Pro Leu Arg Met Ala Arg Pro Gly Gly Pro Glu His Asn Glu Tyr  
1 5 10 15

Ala Leu Val Ser Ala Trp His Ser Ser Gly Ser Tyr Leu Asp Ser Glu  
20 25 30

Gly Leu Arg His Gln Asp Asp Phe Asp Val Ser Leu Leu Val Cys His  
35 40 45

Cys Ala Ala Pro Phe Glu Glu Gln Gly Glu Ala Glu Arg His Val Leu  
50 55 60

Arg Leu Gln Phe Phe Val Val Leu Thr Ser Gln Arg Glu Leu Phe Pro

166

65						70						75						80					
Arg	Leu	Thr	Ala	Asp	Met	Arg	Arg	Phe	Arg	Lys	Pro	Pro	Arg	Leu	Pro								
				85					90					95									
Pro	Glu	Pro	Glu	Ala	Pro	Gly	Ser	Ser	Ala	Gly	Ser	Pro	Gly	Glu	Ala								
			100					105					110										
Ser	Gly	Leu	Ile	Leu	Ala	Pro	Gly	Pro	Ala	Pro	Leu	Phe	Pro	Pro	Leu								
		115					120					125											
Ala	Ala	Glu	Val	Gly	Met	Ala	Arg	Ala	Arg	Leu	Ala	Gln	Leu	Val	Arg								
		130					135					140											
Leu	Ala	Gly	Gly	His	Cys	Arg	Arg	Asp	Thr	Leu	Trp	Lys	Arg	Leu	Phe								
145					150					155					160								
Leu	Leu	Glu	Pro	Pro	Gly	Pro	Asp	Arg	Leu	Arg	Leu	Gly	Gly	Arg	Leu								
				165					170					175									
Ala	Leu	Ala	Glu	Leu	Glu	Glu	Leu	Leu	Glu	Ala	Val	His	Ala	Lys	Ser								
			180					185					190										
Ile	Gly	Asp	Ile	Asp	Pro	Gln	Leu	Asp	Cys	Phe	Leu	Ser	Met	Thr	Val								
		195					200					205											
Ser	Trp	Tyr	Gln	Ser	Leu	Ile	Lys	Val	Leu	Leu	Ser	Arg	Phe	Pro	Arg								
	210						215					220											
Ala	Val	Ala	Ile	Ser	Lys	Ala	Gln	Thr	Trp	Glu	Leu	Ser	Thr	Trp	Leu								
225					230					235					240								

Arg

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<210> 329
<211> 30
<212> PRT
<213> Homo sapiens
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<400> 329  
Ala Arg Gly Thr Leu Glu Leu Pro Thr Pro Leu Ile Ala Ala His Gln  
1 5 10 15

Leu Tyr Asn Tyr Val Ala Asp His Ala Ser Ser Tyr His Met  
20 25 30

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<210> 330
<211> 37
<212> PRT
<213> Homo sapiens
```

<400> 330

167

Ser His Cys Glu Trp Pro Gly Gln Gly Ala Gln Asn Thr Thr Ser Met  
 1 5 10 15

Pro Trp Cys Arg His Gly Thr Val Leu Ala Pro Thr Trp Thr Leu Arg  
 20 25 30

Asp Phe Asp Thr Arg  
 35

<210> 331

<211> 91

<212> PRT

<213> Homo sapiens

<400> 331

Pro Leu Thr Thr Val Ser His Leu Cys Pro Leu Ser Leu Arg Val Phe  
 1 5 10 15

Thr Ser His Leu Asp Ile Thr Ala Gly His Ser His Arg Asp Asp Thr  
 20 25 30

Trp Val Pro Ile Pro Ala Leu Pro Leu Lys His Leu Arg Pro Pro Ser  
 35 40 45

Ser Pro Phe Ala Leu Gly Pro Trp Val Ser His Pro Leu Met Arg Trp  
 50 55 60

Val Gln Lys Leu Ser His Leu His Ser Asn Pro Gly Thr Gly Phe Ser  
 65 70 75 80

Met Gly Gly Lys Ser Ala Glu Lys Leu Lys Cys  
 85 90

<210> 332

<211> 179

<212> PRT

<213> Homo sapiens

<400> 332

Ser Thr Ala Ala Arg Gly Ala Pro Gly Pro Gly Arg Ala Gly Gly Thr  
 1 5 10 15

Pro Arg Ser Ser Pro Cys Gln Ile His Trp Gly His Arg Pro Pro Ala  
 20 25 30

Gly Leu Leu Pro Ile His Asp Gly Leu Leu Val Pro Glu Pro Asp Gln  
 35 40 45

Ser Ser Pro Lys Pro Leu Pro Gln Ser Cys Arg His Phe Gln Ser Pro  
 50 55 60

Asp Leu Gly Thr Gln Tyr Leu Val Ala Leu Asn Gln Lys Phe Thr Asp  
 65 70 75 80

168

Cys Ser Ala Leu Val Phe Trp Thr Pro Leu Arg Lys Asp Val Ser Glu  
                     85                    90                    95  
 Val Val Phe Arg Glu Ala Leu Pro Val Gln Pro Gln Asp Thr Arg Ser  
                     100                    105                    110  
 Pro Pro Ala Gln Leu Val Ser Thr Tyr His His Leu Glu Ser Val Ile  
                     115                    120                    125  
 Asn Thr Ala Cys Phe Thr Leu Leu Asp Pro Pro Pro Leu Lys Gly Val  
                     130                    135                    140  
 Asp Trp Thr Thr Glu Cys His Cys Ser Leu Asn His Gly Pro Thr Arg  
                     145                    150                    155                    160  
 Leu Pro Ala Arg Gly Arg Thr Asp Gln Pro Phe Trp Ala Pro Gly Gln  
                     165                    170                    175  
 Ala Arg His

<210> 333  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<400> 333  
 His Gln Arg Leu Cys Asn Tyr Val Leu Arg Val Cys Cys Pro Ser Leu  
   1                    5                    10                    15  
 Ala Ala Gly Thr Ala Leu Pro Lys His Pro Gln Pro Leu Thr His Pro  
                     20                    25                    30  
 Gly Leu Gln Arg Val Arg Ser Thr Pro Arg Thr Pro Trp Ala Leu Leu  
                     35                    40                    45  
 Gly Tyr Ser Phe Arg Pro Pro Trp  
                     50                    55

<210> 334  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 334  
 Pro Gly Gly Pro Glu His Asn Glu Tyr Ala Leu Val Ser Ala Trp His  
   1                    5                    10                    15  
 Ser Ser Gly Ser Tyr Leu Asp Ser Glu Gly Leu Arg  
                     20                    25

169

<210> 335  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 335  
Asp Val Ser Leu Leu Val Cys His Cys Ala Ala Pro Phe Glu Glu Gln  
1 5 10 15  
Gly Glu Ala Glu Arg His Val Leu Arg  
20 25

<210> 336  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 336  
Arg Leu Thr Ala Asp Met Arg Arg Phe Arg Lys Pro Pro Arg Leu Pro  
1 5 10 15  
Pro Glu Pro Glu Ala Pro Gly Ser Ser Ala Gly Ser  
20 25

<210> 337  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 337  
Gly Glu Ala Ser Gly Leu Ile Leu Ala Pro Gly Pro Ala Pro Leu Phe  
1 5 10 15  
Pro Pro Leu Ala Ala Glu Val Gly Met  
20 25

<210> 338  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 338  
Thr Leu Trp Lys Arg Leu Phe Leu Leu Glu Pro Pro Gly Pro Asp Arg  
1 5 10 15  
Leu Arg Leu Gly Gly Arg Leu  
20

<210> 339  
<211> 28  
<212> PRT

<213> Homo sapiens

<400> 339

Leu Ala Glu Leu Glu Glu Leu Leu Glu Ala Val His Ala Lys Ser Ile  
1 5 10 15

Gly Asp Ile Asp Pro Gln Leu Asp Cys Phe Leu Ser  
20 25

<210> 340

<211> 197

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (97)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 340

Phe Gln Leu Tyr Phe Asn Pro Glu Leu Ile Phe Lys His Phe Gln Ile  
1 5 10 15

Trp Arg Leu Ile Thr Asn Phe Leu Phe Phe Gly Pro Val Gly Phe Asn  
20 25 30

Phe Leu Phe Asn Met Ile Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu  
35 40 45

Glu Gly Ser Phe Arg Gly Arg Thr Ala Asp Phe Val Phe Met Phe Leu  
50 55 60

Phe Gly Gly Phe Leu Met Thr Leu Phe Gly Leu Phe Val Ser Leu Val  
65 70 75 80

Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val Trp Ser Arg  
85 90 95

Xaa Asn Pro Tyr Val Arg Met Asn Phe Phe Gly Leu Leu Asn Phe Gln  
100 105 110

Ala Pro Phe Leu Pro Trp Val Leu Met Gly Phe Ser Leu Leu Leu Gly  
115 120 125

Asn Ser Ile Ile Val Asp Leu Leu Gly Ile Ala Val Gly His Ile Tyr  
130 135 140

Phe Phe Leu Glu Asp Val Phe Pro Asn Gln Pro Gly Gly Ile Arg Ile  
145 150 155 160

Leu Lys Thr Pro Ser Ile Leu Lys Ala Ile Phe Asp Thr Pro Asp Glu  
165 170 175

Asp Pro Asn Tyr Asn Pro Leu Pro Glu Glu Arg Pro Gly Gly Phe Ala

171

180

185

190

Trp Gly Glu Gly Gln  
195

&lt;210&gt; 341

&lt;211&gt; 108

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 341

Gly Val Gly Gln Ala Thr Val Gly Lys Met Ala Tyr Gln Ser Leu Arg  
1 5 10 15

Leu Glu Tyr Leu Gln Ile Pro Pro Val Ser Arg Ala Tyr Thr Thr Ala  
20 25 30

Cys Val Leu Thr Thr Ala Ala Val Gln Leu Glu Leu Ile Thr Pro Phe  
35 40 45

Gln Leu Tyr Phe Asn Pro Glu Leu Ile Phe Lys His Phe Gln Ile Trp  
50 55 60

Arg Leu Ile Thr Asn Phe Leu Phe Phe Gly Pro Val Gly Phe Asn Phe  
65 70 75 80

Leu Phe Asn Met Ile Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu Glu  
85 90 95

Gly Ser Phe Arg Gly Arg Thr Ala Asp Phe Val Phe  
100 105

&lt;210&gt; 342

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 342

Leu Ile Phe Lys His Phe Gln Ile Trp Arg Leu Ile Thr Asn Phe Leu  
1 5 10 15

Phe Phe Gly Pro Val Gly Phe  
20

&lt;210&gt; 343

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 343

Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu Glu Gly Ser Phe Arg Gly  
1 5 10 15

Arg Thr Ala Asp Phe Val Phe Met Phe  
20 25

<210> 344  
<211> 23  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (19)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 344  
Leu Val Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val Trp  
1 5 10 15

Ser Arg Xaa Asn Pro Tyr Val  
20

<210> 345  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 345  
Val Leu Met Gly Phe Ser Leu Leu Leu Gly Asn Ser Ile Ile Val Asp  
1 5 10 15

Leu Leu Gly Ile Ala  
20

<210> 346  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 346  
Asn Gln Pro Gly Gly Ile Arg Ile Leu Lys Thr Pro Ser Ile Leu Lys  
1 5 10 15

Ala Ile Phe Asp Thr Pro Asp Glu Asp  
20 25

<210> 347  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 347



173

Arg Leu Glu Tyr Leu Gln Ile Pro Pro Val Ser Arg Ala Tyr Thr Thr  
 1 5 10 15

Ala Cys Val Leu Thr Thr Ala Ala Val Gln Leu Glu  
 20 25

&lt;210&gt; 348

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 348

Arg Leu Ile Thr Asn Phe Leu Phe Phe Gly Pro Val Gly Phe Asn Phe  
 1 5 10 15

Leu Phe Asn Met Ile Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu  
 20 25 30

&lt;210&gt; 349

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 349

His Ala Ser Ala Gly Pro Asp Gly Ser Ser Pro Ala  
 1 5 10

&lt;210&gt; 350

&lt;211&gt; 115

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 350

Glu Leu Leu Leu Glu Lys Pro Lys Pro Trp Gln Pro Pro Ala Ala Ala  
 1 5 10 15

Pro His Arg Ala Leu Leu Val Leu Cys Tyr Ser Ile Val Glu Asn Thr  
 20 25 30

Cys Ile Ile Thr Pro Thr Ala Lys Ala Trp Lys Tyr Met Glu Glu Glu  
 35 40 45

Ile Leu Gly Phe Gly Lys Ser Val Cys Asp Ser Leu Gly Arg Arg His  
 50 55 60

Met Ser Thr Cys Ala Leu Cys Asp Phe Cys Ser Leu Lys Leu Glu Gln  
 65 70 75 80

Cys His Ser Glu Ala Ser Leu Gln Arg Gln Gln Cys Asp Thr Ser His  
 85 90 95

Lys Thr Pro Phe Ala Ala Pro Cys Leu Pro Pro Arg Ala Cys Pro Ser

174

100

105

110

Ala Thr Arg  
115

<210> 351  
<211> 77  
<212> PRT  
<213> Homo sapiens

<400> 351  
Leu Pro Gly Trp Gly Phe Pro Thr Lys Ile Cys Asp Thr Asp Tyr Ile  
1 5 10 15  
Gln Tyr Pro Asn Tyr Cys Ser Phe Lys Ser Gln Gln Cys Leu Met Arg  
20 25 30  
Asn Arg Asn Arg Lys Val Ser Arg Met Arg Cys Leu Gln Asn Glu Thr  
35 40 45  
Tyr Ser Ala Leu Ser Pro Gly Lys Ser Glu Asp Val Val Leu Arg Trp  
50 55 60  
Ser Gln Glu Phe Ser Thr Leu Thr Leu Gly Gln Phe Gly  
65 70 75

<210> 352  
<211> 65  
<212> PRT  
<213> Homo sapiens

<400> 352  
Ser Pro Val Leu Leu Pro Ala Phe Pro Pro Leu Pro Val Pro Leu Leu  
1 5 10 15  
Ala Leu Pro Val Ser Ala Pro Leu Pro Ala Cys Val Leu Val Ser Ala  
20 25 30  
Pro Ala Cys Ala Pro Leu Leu Ala Pro Ala Cys Ala Leu Ala Leu Ala  
35 40 45  
Pro Gly Phe Pro Gly Thr Arg Arg Ile Val Gly Ala Leu Pro Arg Cys  
50 55 60  
Cys  
65

<210> 353  
<211> 35  
<212> PRT  
<213> Homo sapiens

175

&lt;400&gt; 353

Leu Leu Val Leu Cys Tyr Ser Ile Val Glu Asn Thr Cys Ile Ile Thr  
1 5 10 15

Pro Thr Ala Lys Ala Trp Lys Tyr Met Glu Glu Glu Ile Leu Gly Phe  
20 25 30

Gly Lys Ser  
35

&lt;210&gt; 354

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 354

Leu Lys Leu Glu Gln Cys His Ser Glu Ala Ser Leu Gln Arg Gln Gln  
1 5 10 15

Cys Asp Thr Ser His Lys Thr Pro Phe Ala  
20 25

&lt;210&gt; 355

&lt;211&gt; 40

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 355

Gln Val Ser Gly Leu Ile Leu Ser Leu Ser Cys Gly Met Asp Gly Leu  
1 5 10 15

Ala Leu Asp Gly Ser Pro Ser Pro Ser Pro Xaa Thr Glu Lys Ala Gly  
20 25 30

Arg Cys Ile Ser Gln Thr Ser Leu  
35 40

&lt;210&gt; 356

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

176

&lt;400&gt; 356

Gln Val Ser Gly Leu Ile Leu Ser Leu Ser Cys Gly Met Asp Gly Leu  
 1 5 10 15

Ala Leu Asp Gly Ser Pro Ser Pro Ser Pro Xaa Thr Glu Lys Ala Gly  
 20 25 30

Arg Cys Ile Ser Gln Thr Ser Leu Pro Gly Lys Trp Glu Val  
 35 40 45

&lt;210&gt; 357

&lt;211&gt; 173

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (118)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 357

Arg Ala Ser Lys Thr Val Pro Arg Met Pro Pro Asn Trp Pro Ala Lys  
 1 5 10 15

Met Pro Cys Leu Cys His Ile Arg Thr Val Glu His Leu Gly Thr Ile  
 20 25 30

Ser Ser Gly Ala Pro Gly Arg Pro Thr Gly Gln Gln Ala Ala Arg Thr  
 35 40 45

Tyr His Ile Cys Trp Ile His Pro Gly Gln Lys Ile Asp Ser Leu Pro  
 50 55 60

Pro Ser Ser Gln His Pro Arg Ser Gln Gln Leu Ala Pro Gly Thr Trp  
 65 70 75 80

Pro Ser Thr Ser Thr Thr Lys Pro Ala Glu Glu Thr Leu Gly Ser Ser  
 85 90 95

Ala Ser Leu Pro Ile Ser Gln Ala Arg Lys Ser Glu Lys Cys Thr Phe  
 100 105 110

Gln Pro Ser Pro Trp Xaa Val Arg Gly Lys Glu Ser His Gln Val Pro  
 115 120 125

Ala His Pro Ser His Arg Thr Glu Thr Glu Ser Asp His Ser Pro Val  
 130 135 140

Arg Lys Pro Pro Ser Arg Gly Thr Arg Thr Gly Asp Phe Thr Val Gly  
 145 150 155 160

Asp Trp Ser Glu Ala Trp Leu Leu Glu Leu Ala Leu Leu  
 165 170

<210> 358

<211> 23

<212> PRT

<213> Homo sapiens

<400> 358

Arg Met Pro Pro Asn Trp Pro Ala Lys Met Pro Cys Leu Cys His Ile  
1 5 10 15

Arg Thr Val Glu His Leu Gly  
20

<210> 359

<211> 25

<212> PRT

<213> Homo sapiens

<400> 359

Gly Arg Pro Thr Gly Gln Gln Ala Ala Arg Thr Tyr His Ile Cys Trp  
1 5 10 15

Ile His Pro Gly Gln Lys Ile Asp Ser  
20 25

<210> 360

<211> 25

<212> PRT

<213> Homo sapiens

<400> 360

Trp Pro Ser Thr Ser Thr Thr Lys Pro Ala Glu Glu Thr Leu Gly Ser  
1 5 10 15

Ser Ala Ser Leu Pro Ile Ser Gln Ala  
20 25

<210> 361

<211> 23

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (13)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 361

Lys Ser Glu Lys Cys Thr Phe Gln Pro Ser Pro Trp Xaa Val Arg Gly  
1 5 10 15

Lys Glu Ser His Gln Val Pro

20

<210> 362  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 362  
Lys Pro Pro Ser Arg Gly Thr Arg Thr Gly Asp Phe Thr Val Gly Asp  
1 5 10 15

Trp Ser Glu Ala Trp Leu Leu Glu  
20

<210> 363  
<211> 10  
<212> PRT  
<213> Homo sapiens

<400> 363  
Pro Cys Ala Asp Cys Leu Ser Ala Trp Ala  
1 5 10

<210> 364  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 364  
His Ala Ser Gly Tyr Leu Cys Ile Val Leu Leu  
1 5 10

<210> 365  
<211> 34  
<212> PRT  
<213> Homo sapiens

<400> 365  
Asn Ser Ala Arg Ala Ala Arg Ala Glu Ile Val Leu Gly Leu Leu Val  
1 5 10 15

Trp Thr Leu Ile Ala Gly Thr Glu Tyr Phe Arg Val Pro Ala Phe Gly  
20 25 30

Trp Val

<210> 366  
<211> 22  
<212> PRT

<213> Homo sapiens

<400> 366

Pro Cys Ser Pro Pro Asp Ser Pro Pro Leu Pro Gly Ala Phe Val Trp  
1 5 10 15

Arg Val Leu Trp Val Cys  
20

<210> 367

<211> 25

<212> PRT

<213> Homo sapiens

<400> 367

Ala Arg Ala Cys Phe Ala Tyr Asn Gly Val Cys Ser Glu Gly Arg Cys  
1 5 10 15

Trp Asp Ser His Phe His Gly Ser Val  
20 25

<210> 368

<211> 100

<212> PRT

<213> Homo sapiens

<400> 368

Met Ser Asn Met Gly Lys Ile Pro Ser Leu Ser Leu His Ile Pro Ile  
1 5 10 15

Asn Lys Tyr Ile Cys Ser Arg Ile Pro Lys Phe Ile Gln Lys Val Asn  
20 25 30

Lys Ser Thr Val Leu Gln Ile Cys Leu Lys Arg Gln Ile Ile Leu Asn  
35 40 45

Lys Asn Lys Met Ser Asp His Ser Lys Ile Gly Lys Ala Asn Leu Val  
50 55 60

Gln Ile Asp Ile His Ser Leu Gly Ile Val Glu Thr Gly Cys Val Pro  
65 70 75 80

Ser Lys Arg Tyr Cys Thr Leu Leu Thr Glu Gln Ser Gly Phe Pro Phe  
85 90 95

Leu Ser His Pro  
100

<210> 369

<211> 84

<212> PRT

<213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (54)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 369

Met	Ala	Gly	Cys	Cys	Leu	Lys	Leu	Phe	Gly	Val	Leu	Ser	Leu	Cys	Phe
1				5					10					15	

Leu	Cys	Gly	Leu	Ile	Ser	Ile	Glu	Arg	Val	Ile	Cys	Asn	Pro	Val	Ser
			20					25					30		

Ala	Asp	Phe	Gln	Val	Ser	Thr	Phe	Cys	Gln	Arg	His	Cys	Leu	Leu	Arg
		35					40					45			

Ser	Lys	Val	Met	Phe	Xaa	Ile	Lys	Gly	Xaa	Thr	Ala	Thr	Ile	Glu	Val
	50					55					60				

Ile	Asn	Glu	Asn	Cys	Thr	Leu	Val	Ala	Ala	Pro	Pro	Ile	Gly	Phe	Pro
65					70					75					80

Ile Xaa Phe Leu

&lt;210&gt; 370

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 370

Met	Ser	Asp	His	Ser	Lys	Ile	Gly	Lys	Ala	Asn	Leu	Val	Gln	Ile	Asp
1				5				10					15		

Ile	His	Ser	Leu	Gly	Ile	Val	Glu	Thr	Gly	Cys	Val	Pro	Ser	Lys	Arg
			20					25					30		

Tyr	Cys	Thr	Leu	Leu	Thr	Glu	Gln	Ser	Gly	Phe	Pro	Phe	Leu	Ser	His
		35					40					45			

Pro



181

<210> 371  
<211> 50  
<212> PRT  
<213> Homo sapiens

<400> 371  
Met Ala Gly Cys Cys Leu Lys Leu Phe Gly Val Leu Ser Leu Cys Phe  
1 5 10 15  
Leu Cys Gly Leu Ile Ser Ile Glu Arg Val Ile Cys Asn Pro Val Ser  
20 25 30  
Ala Asp Phe Gln Val Ser Thr Phe Cys Gln Arg His Cys Leu Leu Arg  
35 40 45  
Ser Lys  
50

<210> 372  
<211> 34  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (4)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (8)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (32)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 372  
Val Met Phe Xaa Ile Lys Gly Xaa Thr Ala Thr Ile Glu Val Ile Asn  
1 5 10 15  
Glu Asn Cys Thr Leu Val Ala Ala Pro Pro Ile Gly Phe Pro Ile Xaa  
20 25 30

Phe Leu

<210> 373  
<211> 65  
<212> PRT  
<213> Homo sapiens

182

&lt;400&gt; 373

Pro Thr Glu Gly Arg Gln Lys Val Leu Lys Thr Phe Thr Val Pro Arg  
 1 5 10 15

Ser Ala Leu Ala Met Thr Lys Thr Ser Thr Cys Ile Tyr His Phe Leu  
 20 25 30

Val Leu Ser Trp Tyr Thr Phe Leu Asn Tyr Tyr Ile Ser Gln Glu Gly  
 35 40 45

Lys Asp Glu Val Lys Pro Lys Ile Leu Ala Asn Gly Ala Arg Trp Lys  
 50 55 60

Tyr  
 65

&lt;210&gt; 374

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 374

Pro Arg Ser Ala Leu Ala Met Thr Lys Thr Ser Thr Cys Ile Tyr His  
 1 5 10 15

Phe Leu Val Leu Ser Trp Tyr Thr Phe Leu Asn Tyr Tyr Ile Ser Gln  
 20 25 30

Glu Gly Lys  
 35

&lt;210&gt; 375

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 375

Pro Thr Glu Gly Arg Gln Lys Val Leu Lys Thr Phe Thr Val Pro Arg  
 1 5 10 15

Ser Ala Leu Ala Met Thr Lys Thr  
 20

&lt;210&gt; 376

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 376

Phe Leu Asn Tyr Tyr Ile Ser Gln Glu Gly Lys Asp Glu Val Lys Pro  
 1 5 10 15

183

Lys Ile Leu Ala Asn Gly Ala Arg Trp Lys Tyr  
                   20                  25

<210> 377  
 <211> 13  
 <212> PRT  
 <213> Homo sapiens

<400> 377  
 Phe Lys Asp Gln Leu Val Tyr Pro Leu Leu Ala Phe Thr  
      1                  5                  10

<210> 378  
 <211> 13  
 <212> PRT  
 <213> Homo sapiens

<400> 378  
 Arg Gln Ala Leu Asn Leu Pro Asp Val Phe Gly Leu Val  
      1                  5                  10

<210> 379  
 <211> 10  
 <212> PRT  
 <213> Homo sapiens

<400> 379  
 Ala Thr Ala Ser His Asp Leu Leu Leu Phe  
      1                  5                  10

<210> 380  
 <211> 97  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (72)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 380  
 Met Ser Ile Asn Ile Cys Leu Met Gln Ser Lys Thr Gln Gly Ser Cys  
      1                  5                  10                  15

Gln Tyr Leu Leu Leu Pro His Pro Val Pro Ile Ile Leu Lys Val Ser  
           20                  25                  30

Thr Val Phe Ser Leu Leu Ser Leu Phe Arg Leu Leu Phe Leu Ser Phe  
           35                  40                  45

Cys Pro His Pro Lys Lys Cys Ser Tyr Leu Leu Lys Tyr Tyr Gly Pro

184

50                      55                      60  
 Leu Glu Gly His Lys Thr Leu Xaa Tyr Leu Arg Thr Asn Leu Gly Val  
 65                      70                      75                      80  
 Ile Gln Pro Pro Leu Arg Met Tyr Ala Ala Glu Asp Cys Asn Gly Ile  
                     85                      90                      95

Gly

<210> 381  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<400> 381  
 Met Ser Ile Asn Ile Cys Leu Met Gln Ser Lys Thr Gln Gly Ser Cys  
 1                      5                      10                      15  
 Gln Tyr Leu Leu Leu Pro His Pro Val Pro Ile Ile Leu Lys Val Ser  
                     20                      25                      30  
 Thr Val Phe Ser Leu Leu Ser Leu Phe Arg Leu Leu Phe Leu  
                     35                      40                      45

<210> 382  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (26)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 382  
 Ser Phe Cys Pro His Pro Lys Lys Cys Ser Tyr Leu Leu Lys Tyr Tyr  
 1                      5                      10                      15  
 Gly Pro Leu Glu Gly His Lys Thr Leu Xaa Tyr Leu Arg Thr Asn Leu  
                     20                      25                      30  
 Gly Val Ile Gln Pro Pro Leu Arg Met Tyr Ala Ala Glu Asp Cys Asn  
                     35                      40                      45

Gly Ile Gly  
 50

<210> 383  
 <211> 23  
 <212> PRT

185

&lt;213&gt; Homo sapiens

&lt;400&gt; 383

Lys Glu Glu Asp Asp Asp Thr Glu Arg Leu Pro Ser Lys Cys Glu Val  
1 5 10 15

Cys Lys Leu Leu Ser Thr Glu  
20

&lt;210&gt; 384

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 384

Lys Glu Glu Asp Asp Asp Thr Glu Arg Leu Pro Ser Lys Cys Glu Val  
1 5 10 15

Cys Lys Leu Leu Ser Thr Glu  
20

&lt;210&gt; 385

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 385

Leu Gln Ala Glu Leu Ser Arg Thr Gly Arg Ser Arg Glu Val Leu Glu  
1 5 10 15

Leu Gly Gln

&lt;210&gt; 386

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 386

Leu Gln Ala Glu Leu Ser Arg Thr Gly Arg Ser Arg Glu Val Leu Glu  
1 5 10 15

Leu Gly Gln

&lt;210&gt; 387

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 387

186

Arg Gln Ala Val Ile Val Cys Arg Arg Arg Phe Val  
 1 5 10

&lt;210&gt; 388

&lt;211&gt; 148

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

Pro Pro Arg Trp Ala His Pro Lys Ala Pro Glu Gly Ser Pro Asp Pro  
 1 5 10 15

Pro Ser Pro Pro Ser Ala Leu Gly Leu Ser Val Leu Pro Trp Ser Asp  
 20 25 30

Ser Asp Pro Trp His Ile Ser Val Ser Pro Cys Ala Gln Arg Glu His  
 35 40 45

Tyr Ser Pro Gly Ser Ala His Ile Asn Ser Leu Arg Pro Leu Pro Ala  
 50 55 60

Leu Ser Leu Lys Arg Cys Lys Ala Arg Val Ser Ser Ser Cys Leu Tyr  
 65 70 75 80

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Glu Ile Asp Arg Cys Asp  
 85 90 95

Ser Val Pro Pro Val Ala Leu Cys Ser Ala Ala Tyr Thr Leu Arg Ile  
 100 105 110

Cys Trp Ala Ser Val Leu Cys His Arg Pro Pro Pro Ser Thr Ser Gln  
 115 120 125

Pro Lys Pro Arg Ala Arg Pro Lys Lys Gly Lys Ala Ile Phe Pro Thr  
 130 135 140

Ala Gln Val Pro  
 145

&lt;210&gt; 389

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

Pro Pro Arg Trp Ala His Pro Lys Ala Pro Glu Gly Ser Pro Asp Pro  
 1 5 10 15

Pro Ser Pro Pro Ser Ala Leu Gly Leu Ser Val Leu Pro Trp Ser Asp  
 20 25 30

Ser Asp Pro Trp His Ile Ser Val Ser Pro Cys Ala Gln Arg Glu His  
 35 40 45

Tyr Ser Pro Gly Ser Ala His Ile Asn Ser Leu Arg Pro Leu Pro Ala  
 50 55 60

Leu Ser Leu Lys Arg Cys Lys  
 65 70

<210> 390  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<400> 390  
 Ala Arg Val Ser Ser Ser Cys Leu Tyr Pro Ala Pro Ala Pro Ala Pro  
 1 5 10 15

Ala Pro Leu Glu Ile Asp Arg Cys Asp Ser Val Pro Pro Val Ala Leu  
 20 25 30

Cys Ser Ala Ala Tyr Thr Leu Arg Ile Cys Trp Ala Ser Val Leu Cys  
 35 40 45

His Arg Pro Pro Pro Ser Thr Ser Gln Pro Lys Pro Arg Ala Arg Pro  
 50 55 60

Lys Lys Gly Lys Ala Ile Phe Pro Thr Ala Gln Val Pro  
 65 70 75

<210> 391  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 391  
 Glu Glu Lys Leu Phe Thr Ser Ala Pro Gly Arg Asp Phe Trp Val Met  
 1 5 10 15

Gly Glu Thr Arg Asp Gly Asn Glu Glu Asn  
 20 25

<210> 392  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<400> 392  
 Gln Lys Pro Thr Phe Ala Leu Gly Glu Leu Tyr Pro Pro Leu Ile Asn  
 1 5 10 15

Leu Trp Glu Ala Gly Lys Glu Lys Ser Thr Ser Leu Lys Val Lys Ala  
 20 25 30

Thr Val Ile Gly Leu Pro Thr Asn Met Ser  
35 40



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/05804

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5; 435/320.1, 252.3, 69.1, 6, 7.1; 530/300, 388.22; 514/2; 436/501

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database EST: Accession No.:AA331279. ADAMS et al. Initial assessment of human gene diversity and expression patterns based upon 83 million nucleotides of cDNA sequence. Nature 377 (6547 Suppl), 3-174 (1995). Nucleotides 1-314.	1-12, 14-21
A	SCHWARTING, R. et al. Biochemical characterization and purification of human B Cell Stimulatory Factor (BSF). Eur. J. Immunol. 1985, Vol. 15, pages 632-637, see entire document.	1-21

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 JUNE 1999

Date of mailing of the international search report

07 JUL 1999

 Name and mailing address of the ISA/US  
 Commissioner of Patents and Trademarks  
 Box PCT  
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

EILEEN O'HARA

Telephone No. (703) 308-0196

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/05804

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/05804

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07H 21/04; C07K 1/00, 16/00; C12N 15/00, 1/20; C12P 21/06; A61K 38/00; C12Q 1/68; G01N 33/53, 33/566

## A. CLASSIFICATION OF SUBJECT MATTER: US CL :

536/23.5; 435/320.1, 252.3, 69.1, 6, 7.1; 530/300, 388.22; 514/2; 436/501

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

SEQUENCE DATA BASE MPSRCH: EST, GenEmbl, N\_Geneseq\_34, Issued Patents\_NA, SPTREMBL\_8, SwissProt\_36, PIR\_58, Issued Patents\_AA, (SEQ ID NOS: 11 and 108 only). One nucleotide sequence and one amino acid sequence have been searched. It is not clear which sequences are embraced by the claims because the claims refer to sequences X and Y. The table at pages 180-188 contains many sequences X and Y, yet the claims refer to X and Y in the singular only. Accordingly, the first X nucleotide sequence disclosed and the first Y amino acid sequence disclosed were searched.

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-21, drawn to nucleic acid molecules, vectors, host cells containing recombinant nucleic acid molecules, polypeptides, antibodies, a method of producing a polypeptide, a method for treating a medical condition comprising administering a polypeptide, a method of diagnosing a pathological condition by genetic analysis or protein assay, and a method for identifying a binding partner to a polypeptide, for gene 1, the nucleic acid molecule identified by SEQ ID NO:11, and the polypeptide identified by SEQ ID NO: 108, as listed in the table on pages 180-188 of the description. Groups II through XCV, claims 1-21 for each group, drawn to nucleic acid molecules, vectors, host cells containing recombinant nucleic acid molecules, polypeptides, antibodies, a method of producing a polypeptide, a method for treating a medical condition comprising administering a polypeptide, a method of diagnosing a pathological condition by genetic analysis or protein assay, and a method for identifying a binding partner to a polypeptide for, genes 2 through 95, the nucleic acid molecules identified by SEQ ID NOS:12 through 105, and the polypeptides identified by SEQ ID NOS:109 through 202 respectively, as listed in the table on pages 180-188 of the description.

The inventions listed as Groups I through XCV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Pursuant to 37 C.F.R. § 1.475(b-d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto.

Pursuant to 37 C.F.R. § 1.475(b-d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first recited product, a polynucleotide comprising gene No. 1, identified by SEQ ID NO:11, the polypeptide it encodes, identified by SEQ ID NO:108, methods of producing the polypeptide, and methods of using the polynucleotide and polypeptide. Further pursuant to 37 C.F.R. § 1.475(b-d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

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